Journal of
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LONDON: THE CHEMICAL SOCIETY, BURLINGTON HOUSE, W.1

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THE CHEMICAL SOCIETY

ANNIVERSARY MEETINGS

Edinburgh—March 29th and 30th, 1950

Wednesday, March 29th.

11 a.m.	The Presidential Address, "The Chemical Society—A Mid-Century Review," by Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S. To be delivered in the Chemistry Department, King's Buildings.
12 noon.	The 109th ANNUAL GENERAL MEETING.
2 p.m.	Coach tours have been arranged as follows:

1. Edinburgh, Cramond Bridge, Forth Bridge. The party will cross on the Ferryboat and return to South Queensferry (tea at The Hawes Inn), Kirkliston, Turnhouse, Edinburgh.
2. Edinburgh, Dalkeith, Lauder, Earlston, Leaderfoot, Sir Walter Scott's View, Bemersyde, Dryburgh Abbey (tea at Dryburgh Abbey Hotel), Mertoun Bridge, St. Boswell's, Leaderfoot, Newstead, Melrose, Abbotsford, Galashiels, Innerleithen, Peebles, Eddleston, Leadburn, Edinburgh.

8.30 p.m.	Reception by the University of Edinburgh in the University Library.

Thursday, March 30th.

10 a.m.	Annual Meeting of Local Representatives—King's Buildings Common Room.
11.30 a.m.	Faraday Lecture, "The Application of Radioactive Indicators in Biochemical Studies," by Professor G. Hevesy, For.Mem.R.S., Honorary Fellow. To be held in the Zoology Department, King's Buildings. The Lecture will be followed by the presentation of the Faraday Medal to the Lecturer.
7 p.m. for 7.30.	Anniversary Dinner at which the new President of the Society will be formally installed. To be held at the North British Station Hotel.

Further particulars and forms of application for tickets are being sent to Fellows.

The Royal Institute of Chemistry

Fellows of the Society attending the Anniversary Meetings of the Royal Institute of Chemistry on March 31st and April 1st can reach Glasgow by the following trains.

Depart	Edinburgh (Waverley)	8.10 a.m.	9.5 a.m.
Arrive	Glasgow	9.20 a.m.	10.8 a.m.

SCIENTIFIC MEETINGS DURING MARCH AND APRIL, 1950

LONDON.

Thursday, March 2nd, 1950, at 7.15 p.m.

Centenary Lecture, **The Azulenes,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the Main Chemistry Lecture Theatre, The Imperial College of Science and Technology, S.W.7.

Thursday, March 16th, 1950, at 7.15 p.m.

The following papers will be read and discussed:

"The significance of the bromine cation in aromatic substitution. Parts I and II." By D. H. Derbyshire and W. A. Waters.

"The kinetics of aromatic halogen substitution. Part VII. Nitrobenzene and azobenzene." By P. W. Robertson, T. R. Hitchings, and G. M. Will.

"The effect of bond structure on the transformation of *o*-aroyloxyacetoarones into *o*-hydroxydiaroylmethanes—Baker–Venkataraman transformation." By N. V. Nowlan, P. A. Slavin, and T. S. Wheeler.

To be held at Burlington House, W.1.
Abstracts of the papers may be obtained from the General Secretary.

ABERDEEN.

Thursday, March 9th, 1950, at 7.30 p.m.

Lecture, **The Chemistry of Anæsthetics,** by Professor H. B. Nisbet, D.Sc., F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Chemistry Department, Marischal College, Aberdeen.

BIRMINGHAM.

Friday, March 17th, 1950, at 4.30 p.m.

Lecture, **How Crystals Grow,** by Professor E. K. Rideal, M.B.E., M.A., D.Sc., F.R.S.

To be held in the Main Chemical Lecture Theatre, Chemistry Department, The University, Edgbaston, Birmingham.

EDINBURGH.

Thursday, March 16th, 1950, at 7.30 p.m.

Lecture, **Some Aspects of Photo-oxidation with Reference to Chlorophyll,** by Dr. M. Ritchie.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the North British Station Hotel, Edinburgh.

EIRE.

Wednesday, March 1st, 1950, at 7.45 p.m.

Lecture, **Deoxy-sugars and Nucleic Acids,** by Professor M. Stacey, D.Sc., F.R.I.C.

Joint meeting with the Irish Chemical Association, the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Department of Chemistry, University College, Dublin.

Friday, March 3rd, 1950, at 7.45 p.m.

Lecture, **Bacterial Nucleic Acids,** by Professor M. Stacey, D.Sc., F.R.I.C.

Joint meeting with the Irish Chemical Association, the Royal Institute of Chemistry, and the Society of Chemical Industry, to be held at University College, Cork.

Monday, March 6th, 1950, *at* 7.45 *p.m.*

Lecture, **Deoxy-sugars and Nucleic Acids,** by Professor M. Stacey, D.Sc., F.R.I.C.

Joint meeting with the Irish Chemical Association, the Royal Institute of Chemistry, and the Society of Chemical Industry, to be held in the Chemical Laboratories, University College, Galway.

Wednesday, March 8th, 1950, *at* 7.45 *p.m.*

Lecture, **Lycomarasmin : The Chemistry of Wilting Diseases,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the Department of Chemistry, Trinity College, Dublin.

GLASGOW.

Friday, March 10th, 1950, *at* 7.15 *p.m.*

Lecture, **Purine Synthesis—A New Chapter,** by Dr. A. H. Cook, F.R.I.C.

Joint meeting with local Chemical Societies, to be held in the Chemistry Department, The University, Glasgow.

HULL.

Thursday, March 2nd, 1950, *at* 6 *p.m.*

Lecture, **Aromatic Nitration,** by Dr. G. M. Bennett, C.B., M.A., F.R.S.

Joint meeting with the Royal Institute of Chemistry, to be held at University College, Hull.

LIVERPOOL.

Tuesday, March 7th, 1950, *at* 4.30 *p.m.*

Lecture, **Lycomarasmin : The Chemistry of Wilting Diseases,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the Chemistry Department, The University, Liverpool.

Thursday, March 16th, 1950, *at* 4.30 *p.m.*

Lecture, **Heterogeneous Catalysis,** by Professor E. K. Rideal, M.B.E., M.A., D.Sc., F.R.S.

To be given in the Chemistry Lecture Theatre, The University, Liverpool.

Thursday, March 23rd, 1950, *at* 4.30 *p.m.*

Lecture, **Photo-excited Electron-transfer Reactions,** by Professor M. G. Evans, D.Sc., F.R.S.

To be given in the Chemistry Lecture Theatre, The University, Liverpool.

(*Note* : Professor Evans' Lecture has been postponed from March 16th to 23rd.)

MANCHESTER.

Friday, March 3rd, 1950, *at* 6.30 *p.m.*

Centenary Lecture, **The Azulenes,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the University, Manchester.

Thursday, March 9th, 1950, *at* 6.30 *p.m.*

Pedler Lecture, **Polycyclic Aromatic Hydrocarbons,** by Professor J. W. Cook, D.Sc., Ph.D., F.R.S.

To be given in the Chemistry Department, The University, Manchester.

Wednesday, March 22nd, 1950, at 6.30 p.m.

Lecture, **Some Recent Applications of Infra-red Spectroscopy,** by Dr. H. W. Thompson, M.A., F.R.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held at the Engineer's Club, Manchester.

NORTHERN IRELAND.

Friday, March 10th, 1950, at 7.30 p.m.

Lecture, **Inorganic Chromatography,** by Mr. R. A. Wells, B.Sc., A.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Agricultural Lecture Theatre, Elmwood Avenue, Belfast.

NOTTINGHAM.

Thursday, March 9th, 1950, at 6.30 p.m.

Lecture, **Some Aspects of Structural Chemistry,** by Professor W. Wardlaw, C.B.E., D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society, to be held in the Lecture Theatre, Department of Chemistry, The University, Nottingham.

ST. ANDREWS and DUNDEE.

Thursday, April 13th, 1950, at 5 p.m.

Lecture, **Chemical Reactions Induced by Nuclear Radiations,** by Dr. F. S. Dainton, M.A.

To be given in the Chemistry Department, University College, Dundee.

SHEFFIELD.

Thursday, March 16th, 1950, at 5.30 p.m.

Lecture, **Recent Developments in Acetylene Chemistry,** by Professor E. R. H. Jones, D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society, to be held in the Chemistry Lecture Theatre, The University, Sheffield.

Thursday, April 27th, 1950, at 5.30 p.m.

Lecture, **Recent Advances in the Chemistry of the Steroids,** by Professor F. S. Spring, D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society, to be held in the Chemistry Lecture Theatre, The University, Sheffield.

SOUTHAMPTON

Friday, March 3rd, 1950, at 5 p.m.

Lecture, **The Determination of Traces of Elements and Compounds,** by Dr. H. Irving, M.A., F.R.I.C.

Joint meeting with University College Chemical Society, to be held in the Physics Department, University College, Southampton.

Wednesday, April 26th, 1950, at 7 p.m.

Lecture, **Trace Elements in Plant Life,** by Dr. W. A. Roach, A.R.C.S., A.R.I.C.

Joint meeting with Mid-Southern Counties Section of the Royal Institute of Chemistry and Portsmouth and District Chemical Society, to be held at the Municipal College, Portsmouth.

SOUTH WALES.

Friday, March 3rd, 1950, at 5.30 p.m.

Lecture, **Synthetical Investigations in the Series of Cyclic Imines,** by Professor F. E. King, M.A., D.Phil.

Joint meeting with University College of Swansea Students' Chemical Society, to be held in University College, Swansea.

PROCEEDINGS
OF THE
CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, December 15th, 1949, at 7.15 p.m.

Dr. J. KENYON, F.R.S., Vice-President, was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at the Royal Institution on Wednesday, November 30th, 1949, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: S. K. Hutchinson, E. M. Joiner, A. R. Katritzky, D. J. R. Laurence, A. C. Heathfield, J. Madinaveitia.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed:

"Some Physico-chemical Properties of Acridine Antimalarials with Reference to their Biological Action." By D. H. Hammick and S. F. Mason.

"The Properties of Freshly Formed Surfaces. Parts XI–XIV." By C. C. Addison and S. K. Hutchinson.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
John Evelyn Cave-Brown-Cave (Ilford)	Feb. 7th, 1946.	Nov. 10th, 1949.
Arthur Jenner Chapman (Chalfont St. Giles)...	Dec. 5th, 1895.	Nov. 9th, 1949.
Benedict Trembath Kitto (Gerrard's Cross) ...	Dec. 6th, 1917.	Sept. 1949.

CONGRATULATIONS.

The President has conveyed the congratulations of the Council to the following Fellows whose names appear in the New Year Honours List:

Knight Bachelor

Sidney John Saint

C.B.

Owen Haddon Wansbrough-Jones

C.B.E.

Frederick Hardy,
Frederick George Soper

ELECTION OF NEW FELLOWS.

The following 36 candidates were elected Fellows of the Society on December 15th, 1949:

Arthur Billing Angus.
Morrell Kenneth Aston.
John Dennis Butler.
Josephine Natalie Cartwright.
Denis Michael Comber.
Alexander Latimer Davidson.
Austen Emlyn Davies.
Michael Trevor Davies.
John Owen Dawson.
John Albert Durant.
Dennis Brian Freeman.
Robert Arthur Hall.
Elbert Everett Harris.
Robert Johnston.
David Thomas King.
Mark Long.
Minoo Dossabhoy Mehta.
David Fisher Muggleton.
Derek Payne.
Donald George Peacock.
Peter William Sadler.
Allen W. Scholl.
Raymond B. Seymour.
Kenneth Shorrock.
Shivagangay Siddappa.
Bratislav G. Sunek.
Brian William Stannard.
John Ernest Stone.
Stig Arne Sunnér.
Harry Callender Sutton.
Frederick Maurice Tayler.
Alexander Patrick Tulloch.
William Hughes Wadman.
Charles Wickham-Jones.
Alfred Peter Wolf.
Richard William Young.

MEETING OF COUNCIL.

A meeting of Council was held on December 15th, 1949.

The report of the meeting of the Publication Committee held on November 17th, 1949, was received, and approval was given to a recommendation that, in papers submitted for publication in the Journal, the names of new compounds should henceforth be italicised only in the Experimental section (at their first mention excluding headings). The use of italics in the Introduction and in the Summary will be abandoned.

The thanks of the Council have been conveyed to the Pharmaceutical and Allied Chemicals Disposals Association, Ltd., for a donation towards the cost of publications and to Dr. R. Raper for a gift of the Society's publications.

The reports of the meetings of the Joint Library Committee and the Research Fund Committee held on November 23rd, 1949, were received.

Certain matters of a formal and financial nature were conducted.

CORDAY-MORGAN MEDAL.

The award of the Corday-Morgan Medal in respect of the year 1949 will receive consideration by Council early in 1951. Applications submitted by, or on behalf of, candidates must be received at the Society's apartments in Burlington House, not later than December 31st, 1950. The award consists of a Silver Medal designed by Mr. Percy Metcalfe, C.V.O., and a cash prize amounting to not less than £150.

The following rules govern the award:

1. The Award shall be known as the Corday-Morgan Medal.

2. The Award shall be made annually to the chemist of either sex and of British nationality who, in the judgment of the Council of the Chemical Society, shall have published during the year in question the most meritorious contribution to experimental Chemistry, and who, at the date of publication, shall not have attained the age of thirty-six years. The date of publication of any journal shall be deemed to be the date at which the journal was first available to the public.

3. The Award shall not be made more than once to the same candidate.

4. The Council may at its discretion suspend the Award in any year in which no suitable candidate presents himself or is brought to the notice of the Council. In the event of such suspension a sum equal to the income otherwise available for the Award in that year shall be invested and added to the capital of the Trust Fund.

5. The Award shall consist of a silver medal and a monetary prize amounting to the balance of the income of the Trust Fund for the year, after payment of the expenses incidental to the Award.

6. No restrictions shall be placed upon the branch of chemistry for which the Award is granted, or upon the place in which the work is conducted.

7. The merits of the work of any candidate for the Award may be brought to the notice of the Council either by persons who desire to recommend the candidate or by the candidate himself.

8. Details of the Award shall be published annually in the *Proceedings of the Chemical Society* and elsewhere.

9. Applications, or recommendations for the Award, accompanied by offprints or copies of any published work on which the grant of the Award is to be judged, shall be forwarded so that they shall reach the Society not later than the thirty-first day of December in the year following that for which the Award is to be made.

10. Each candidate shall give the names of two persons with a knowledge of his work, to whom references can be made by the Society.

11. The Award shall be presented at a meeting of the Society.

12. If any doubt shall arise as to the correct interpretation of these rules, the matter shall be decided by the Council of the Chemical Society.

13. The Council may from time to time alter or add to the regulations for the administration of the Award, provided that no regulation shall be approved that is contrary to the terms of the Bequest as expressed in the will of the late Sir Gilbert T. Morgan.

LIBRARY REGULATIONS

The regulations governing the use of the Library of the Chemical Society have been amended by the Joint Library Committee and approved by the Chemical Council. The following are the revised rules:

1. The Library is open from 10 a.m. to 9 p.m. daily, except on Saturdays and from the 16th July to the 30th September, inclusive, when it closes at 5 p.m. The Library is closed on Christmas Eve, Bank Holidays and the day after, and at 1 o'clock on the day preceding Good Friday and Christmas Eve. The times may be varied from time to time, as the Joint Library Committee may determine.

2. Every person on first entering the Library on any day must sign a book provided for the purpose.

3. Silence must be maintained in the Reading Room and smoking is not permitted.

4. No marks of any kind may be made in the Library books or periodicals, and no papers or books may be placed on them.

5. Borrowers are not allowed to have on loan more than six volumes at a time, without special permission from the Librarian.

6. Dictionaries, Pamphlets of which there are not duplicate copies, and certain early chemical and other books belong to the Reference Library, and are not for general circulation. Persons desiring to borrow books from the Reference Library must make special application to the Librarian, who may then, at his discretion, issue such volumes for a period not exceeding one month.

7. Journals of which the Society does not possess duplicate copies may not be borrowed, except for one night, or from Saturday to Monday. The privilege does not extend to volumes of special value or rarity, and will not be continued to any person who does not strictly comply with these conditions.

8. A new book may not be borrowed or bespoken until one month after it has been added to the Library.

9. No reader may remove a book from the Library without filling up and handing to a member of the Library staff one of the loan receipt slips provided for the purpose. This slip will be returned to the borrower on the return of the book.

10. Books are issued to the person desiring the loan, or to anyone bringing a signed order from such person. In either case a receipt must be given on the form provided. When a person desires a book or books to be forwarded, a signed request must be sent to the Librarian and the whole cost of the carriage paid. The Librarian may also issue books in response to a telephoned request from a person entitled to borrow, subject to the con-

ditions that the request is subsequently confirmed in writing, and that the parcel be posted to an address registered with the Librarian. All books borrowed shall be at the risk of the borrower from the moment they are issued or dispatched by the Librarian, and until they are returned to the Librarian. Volumes returned through the post must be securely packed in a box, or otherwise protected to prevent injury.

11. The privilege of borrowing is a personal one, and borrowers are therefore not permitted to re-lend volumes or to borrow them for consultation by others.

12. Books may not be sent or taken out of the British Isles.

13. Borrowers shall be at liberty to retain a book one calendar month, unless, at the expiration of a fortnight, notice is received that the book is required by another person, in which case it must be returned at once. Single parts of journals may not be retained longer than one week. No volume may be re-issued to the same borrower until at least seven days have elapsed after its return, neither may it be transferred by one borrower to another.

14. Borrowers retaining books longer than the time specified, and neglecting to return them when demanded, shall forfeit the right to borrow books from the Library until the volume or volumes be returned, and for such further time as the Joint Library Committee may determine.

15. Persons to whom books have been issued shall be held responsible for their preservation from injury; and if any book when returned is found to have been damaged, the Council of the Chemical Society may order that it be repaired or replaced at the expense of the borrower. In the event of any book being lost or being detained after application has been made for its return, the Council of the Chemical Society may replace, at the cost of the borrower, the volume or volumes so lost or detained, or, if the book cannot be replaced, may require suitable compensation from the borrower. This regulation shall also apply to single parts of periodicals.

16. For the purpose of revision and cleaning, the Library shall be closed for a fortnight in each year, before which time all books must be returned, unless special permission has been previously obtained from the Librarian. In the event of any book not being returned on such occasion, the Council of the Chemical Society may replace it at the cost of the borrower.

17. Persons who are neither members of the Constituent Bodies nor members of contributing Societies, may be permitted to use the Library for reference purposes for a period not exceeding one week, upon the written introduction of a member of a Constituent Body, or upon the production of satisfactory references or recommendations to the Librarian.

18. Violation of any regulation renders the person concerned liable to suspension of Library privileges for such time as the Chemical Council may direct.

RESEARCH GRANTS.

The Council have approved the following grants from the Research Fund:

	£	s.	d.
Cambridge, Laboratory of Physical Chemistry			
Mr. P. Smith. "Polymerisation of acrylonitrile photosensitised by hydrogen peroxide in aqueous solution"	30	0	0
Huddersfield, Technical College			
Dr. G. R. Ramage. "β-Caryophyllene"	20	0	0
Leeds, The University			
Dr. N. H. Hartshorne. "Kinetics of polymorphic change"	25	0	0
Leicester, University College			
Dr. C. Eaborn. "Reactions of organo-silicon compounds"	15	0	0

	£	s.	d.
London, Birkbeck College			
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Dr. Ishbel G. M. Campbell. "Configuration of heterocyclic antimony compounds"	15	15	0
Dr. N. B. Chapman. (*a*) "Kinetics of replacement of halogen atoms in benzenoid and heterocyclic systems." (*b*) "Synthesis of potential histamine antagonists"	30	0	0

Swansea, University College

	£	s.	d.
Mr. R. J. Bridgwater. "Stereochemistry and replacement reactions of the coprostanyl chlorides"	10	0	0
Mr. G. Roberts. "Stereochemistry and replacement reactions of cholesteryl chloride and the cholestanyl chlorides"	10	0	0

CIPHERING SYSTEMS FOR ORGANIC STRUCTURAL FORMULÆ.

The International Union of Pure and Applied Chemistry has appointed a Commission to examine and develop a ciphering system for organic structural formulæ. In receiving the report of this Commission, the British National Committee for Chemistry decided to call the attention of British chemists to the following wish expressed by the Commission: "In order to facilitate full consideration by the Commission before the next Conference of the Union in Washington in 1951, ciphering systems should be submitted before March 1st, 1950, to the Commission's Acting Secretary, Professor J. W. Perry, Room 20–E–215, Massachusetts Institute of Technology, Cambridge 39, Mass., U.S.A. Persons submitting ciphering systems will be asked to demonstrate their effectiveness by applying them to certain tests set up by the Commission."

INTERNATIONAL UNION OF CRYSTALLOGRAPHY.

The Executive Committee of the International Union of Crystallography has accepted a kind invitation from the Swedish National Committee of Crystallography to hold the Second General Assembly and International Congress in Stockholm from June 27th to July 3rd, 1951. These dates have been chosen in consultation with the Swedish National Committee and with the National Committee of each of the Adhering Bodies. It is hoped that this early notice will make it possible for crystallographers throughout the world to arrange to attend.

Further particulars of the meeting will be given from time to time.

INTERNATIONAL CONGRESS ON ANALYTICAL CHEMISTRY—1952.

Plans are now being prepared for an International Congress on Analytical Chemistry to be held in Britain in 1952 under the patronage of the International Union of Chemistry. The Executive Committee, which has had preliminary discussions with regard to the location of the Congress, publication of papers, and other matters, is under the Chairmanship of Mr. G. Taylor, F.R.I.C. The Chairman of the General Committee is Sir Robert Robinson, O.M., P.R.S., and the Honorary Secretary of the Congress is Mr. R. C. Chirnside, F.R.I.C., Research Laboratories of the General Electric Co., Ltd., Wembley.

A further announcement will be made in due course.

AMERICAN CHEMICAL SOCIETY—MEETING ON RUBBER CHEMISTRY.

The Division of Rubber Chemistry of the American Chemical Society is holding an International Meeting in Cleveland, Ohio, U.S.A., on October 11th, 12th, and 13th, 1950. This meeting is open to all scientists and technologists active in the field of rubber.

Papers are invited from members of scientific societies from all countries. Such papers should pertain to the structure of rubber, mechanism of vulcanisation, ageing, etc., polymerisation of synthetic rubbers, study of rubber latex and its applications, and other phases of rubber technology including processing and manufacturing procedures.

Those wishing to submit papers should contact Mr. C. R. Haynes, Secretary of the Division of Rubber Chemistry, Binney and Smith Co., 41 East 42nd Street, New York 17, New York, forwarding an abstract of approximately 400 words describing their papers. All papers must be presented in English. Such abstracts should reach Mr. Haynes before July 1st, 1950.

MEETINGS OUTSIDE LONDON

EIRE.

"The Head-to-tail Isoprene Rule and its Bearing on Terpene Chemistry," by Professor G. R. Clemo, D.Sc., F.R.S.

A joint meeting with the Werner Society was held in the Chemistry Lecture Theatre, Trinity College, Dublin, on November 25th, 1949, with Professor W. Cocker in the Chair.

The lecture was followed by an interesting discussion, and the chairman conveyed the thanks of the meeting to Professor Clemo.

NOTTINGHAM.

Meeting for the reading of original papers.

A joint meeting with the University Chemical Society was held in the Department of Chemistry of the University on December 1st, 1949, with Professor F. E. King in the Chair.

The following papers were read:

"Antituberculous compounds. Part V. 2-Sulphanimilamido-5-alkyl-1 : 3 : 4-oxa- and -thia-diazoles and related isothiosemicarbazones and isothioureas," by J. D. Brooks, P. T. Charlton, P. E. Macey, D. A. Peak, and W. F. Short.

"The crystal structure of a complex between quinol and methyl cyanide," by H. M. Powell and S. C. Wallwork.

Dr. M. W. Partridge, on behalf of those present, warmly thanked Dr. Peak and Mr. Wallwork, who read the papers.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objections to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the Journal for January, 1950. Such objections will be treated as confidential. The forms of application are available in the Library.)

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(List of papers received between December 5th, 1949, and January 6th, 1950.)

"Some heterocyclic *N*-oxides." By P. Mamalis and V. Petrow.

"9 : 10-Dihydrophenanthrenes. Part I. The formation of 9 : 10-dihydrophenanthrenes from 2 : 2′-disubstituted diphenyls." By D. Muriel Hall, Mary S. Lesslie, and E. E. Turner.

"The kinetics of halogen substitution. Part VIII. Halogen addition. Part XV. Benzyl and allyl chloride, bromide, and cyanide." By L. D. Swindale, B. E. Swedlund, and P. W. Robertson.

"The preparation of pure arsenic." By G. A. Geach, R. A. Jeffery, and R. J. Shelton.

"*cyclo*Hexylidene derivatives of mannitol." By E. J. Bourne, W. M. Corbett, and D. Eggleston.

"Amidines. Part XIII. Preparation of 2-substituted 4 : 5-dihydroglyoxalines and ring homologues from substituted amidines and alkylenediamines." By P. Oxley and W. F. Short.

"Steroids and the Walden inversion. Part VI. Reduction of cholest-5-en-3-one with lithium aluminium hydride." By C. W. Shoppee and G. H. R. Summers.

"Aminoalkyl tertiary carbinols and derived products. Part II. 3-Amino-1 : 1-di-2′-thienylalkan-1-ols and -alk-1-enes." By D. W. Adamson.

"The nitration of polystyrene." By H. Zenftman.

"Deoxy-sugars. Part X. Some methanesulphonyl and toluene-*p*-sulphonyl derivatives of ethyl 2 : 3-dideoxy-α-D-glucoside." By S. Laland, W. G. Overend, and M. Stacey.

"Pseudo-metallic bonding of hydrides." By A. R. Ubbelohde.

"The preparation of a series of (±)-*n*-eicosanols and *n*-eicosanones." By Vivienne R. Churchward, N. A. Gibson, R. J. Meakins, and Joan W. Mulley.

"The chemistry of fungi. Part IX. 3 : 4-Dihydrocoumarins." By F. M. Dean, Alexander Robertson, and W. B. Whalley.

"The chemistry of fungi. Part X. The synthesis of 4-hydroxy-3-acetylcoumarins." By G. G. Badcock, F. M. Dean, Alexander Robertson, and W. B. Whalley.

"Attempts to prepare new aromatic systems. Part II. Heptalene." By G. O. Aspinall and Wilson Baker.

"A series of 9-dialkylaminoalkylisoalloxazines." By R. B. Barlow and H. R. Ing.

"Fucoidin. Part I. The isolation and purification of fucoidin from brown seaweeds." By E. G. V. Percival and A. G. Ross.

"Fucoidin. Part II. The hydrolysis of a methylated fucoidin prepared from *Fucus vesiculosus*." By J. Conchie and E. G. V. Percival.

"3 : 4-Dimethyl L-fucose and 2 : 3-dimethyl L-rhamnose." By E. E. Percival and E. G. V. Percival.

"Deoxy-sugars. Part XI. Further observations on the Dische reaction for 2-deoxypentoses." By W. G. Overend, F. Shafizadeh, and M. Stacey.

"The chloro- and iodo-acetates of dihydrolanosterol and dihydroagnosterol." By R. G. Curtis.

"A synthesis of adenine, labelled with ^{14}C." By V. M. Clark and H. M. Kalckar.

"The electrical conductivity of iodine monochloride and iodine trichloride." By N. N. Greenwood and H. J. Emeléus.

"Reactions of ethylene oxides. Part IV. The reaction of epichlorohydrin with some aromatic amines." By W. Davies and W. E. Savige.

"The chemistry of carcinogenic nitrogen compounds. Part IV. New substituted angular benzacridines and dibenzacridines." By Ng.Ph. Buu-Hoï.

"Piperettine from *Piper nigrum*, its isolation, identification, and synthesis." By F. S. Spring and James Stark.

"Decomposition reactions of the aromatic diazo-compounds. Part XII. The reaction between diazo-compounds and potassium ferrocyanide." By M. C. Ford, William A. Waters, and H. T. Young.

"The nitration of *pp'*-dichloroazobenzene." By C. D. Houghton and William A. Waters.

"Some observations on carbon formation in flames." By W. G. Parker and H. G. Wolfhard.

"The reductive dissolution of ferric oxide in acid." Part I. The reductive dissolution of oxide films present on iron." By M. J. Pryor and U. R. Evans.

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"The reductive dissolution of ferric oxide in acid. Part III. The mechanism of reductive dissolution." By M. J. Pryor.

"Quinamine. Part IV. Sulphobenzeneazoquinamine and nitrating oxidation of quinamine to 3 : 6 : 8-trinitro-4-hydroxyquinoline." By (Miss) G. Bendz, C. C. J. Culvenor, L. J. Goldsworthy, K. S. Kirby, and Sir Robert Robinson.

"Aminohydroxynaphthoic acids. Part II. Attempted synthesis of 7-amino-4-hydroxy-2-naphthoic acid ('carboxy-J-acid') from 2-amino-3-naphthoic acid." By W. F. Beech and N. Legg.

"Absorption spectra of substances containing the carbon–iodine bond. Part I." By R. A. Durie, T. Iredale, and J. M. S. Jarvie.

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"Kinetics and mechanism of aromatic nitration. Part II. Nitration by the nitronium ion NO_2^+, derived from nitric acid." By E. D. Hughes, C. K. Ingold, and R. I. Reed.

"Kinetics and mechanism of aromatic nitration. Part III. Nitration in acidified aqueous nitric acid." By E. S. HALBERSTADT, E. D. HUGHES, and C. K. INGOLD.

"Kinetics and mechanism of aromatic nitration. Part IV. Nitration by dinitrogen pentoxide in aprotic solvents." By V. GOLD, E. D. HUGHES, C. K. INGOLD, and G. H. WILLIAMS.

"Kinetics and mechanism of aromatic nitration. Part V. Nitration by acyl nitrates, particularly by benzoyl nitrate." By V. GOLD, E. D. HUGHES, and C. K. INGOLD.

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"Chemistry of nitronium salts. Part I. Isolation of some nitronium salts." By D. R. GODDARD, E. D. HUGHES, and C. K. INGOLD.

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"Amidines. Part XIV. Preparation of 2-substituted 4 : 5-dihydro-oxazoles and -1 : 3-oxazines from hydroxyalkylamines and *N*-substituted amidines or ketoxime sulphonates." By P. Oxley and W. F. Short.

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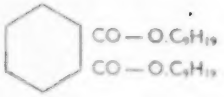

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JOURNAL
OF
THE CHEMICAL SOCIETY

1. *Puberulic and Puberulonic Acids. Part I. The Molecular Formula of Puberulonic Acid and Consideration of Possible Benzenoid Structures for the Acids.*

By R. E. Corbett, C. H. Hassall, A. W. Johnson, and A. R. Todd.

The molecular formula of puberulonic acid, recorded by earlier workers as $C_9H_4O_6$, has been revised to $C_9H_4O_7$. A possible trihydroxyformylbenzoic acid structure for puberulic acid has been shown to be untenable by the non-identity of 2 : 3 : 5-*trihydroxybenzaldehyde* with the decarboxylation product of puberulic acid. Benzenoid formulæ for these acids are therefore excluded.

Puberulic and puberulonic acids were first isolated by Birkinshaw and Raistrick (*Biochem. J.*, 1932, **26**, 441) from cultures of the moulds *Penicillium puberulum* and *P. aurantio-virens* and the formulæ $C_9H_6O_6$ and $C_9H_4O_6$ respectively were assigned to them. Both compounds titrated as dibasic acids, and the almost colourless puberulic acid, m. p. 316—318°, could be separated from mixtures of the two as its diacetyl derivative, m. p. 212°, whereas the yellow puberulonic acid, m. p. 298°, was unaffected by acetylating agents. Puberulic acid formed a tetramethyl derivative with diazomethane, and diacetylpuberulic acid formed a dimethyl derivative under the same conditions, so that the molecule of puberulic acid contained four acidic groups of which at least two were enolic or phenolic hydroxyl groups. No evidence was obtained for the presence of a carbonyl group, and the authors were unable to suggest a satisfactory structure either for puberulic or for puberulonic acid. A little later Barger and Dorrer (*ibid.*, 1934, **28**, 11) carried out a further investigation of the two acids but likewise were unable to advance structural formulæ to explain all of the experimental results. They showed that puberulic acid almost certainly contained a carboxyl group since it readily lost carbon dioxide when heated, yielding a crystalline product, $C_7H_4O_4$. Puberulonic acid changed from yellow through pink to colourless in the course of neutralisation with sodium hydroxide and, on the assumption of a formula $C_9H_4O_6$, irregular values were given for the basicity : a value of 2·3 was obtained when the acid was titrated directly, whereas back titration of alkaline solutions gave values varying from 2·9 to 3·5. This seemed to suggest the presence of a lactone or pseudo-acid grouping. In a footnote to their paper Barger and Dorrer (*loc. cit.*) stated that Dr. Hoyer had obtained evidence that puberulonic acid is structurally related to puberulic acid but the nature of this evidence has never been divulged.

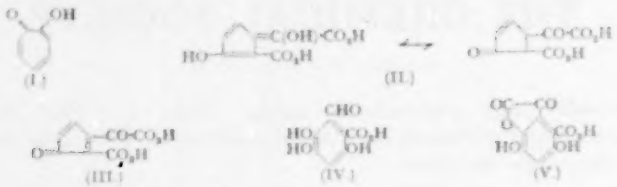
No further work on the chemistry of these compounds has been published. Oxford, Raistrick, and Smith (*Chem. and Ind.*, 1942, **61**, 485) have described the isolation of the same acids from *P. Johanniolí* Zaleski and *P. cyclopium-viridicatum* series and have reported that these mould metabolic products have a significant antibiotic activity against various Gram-positive organisms. Dewar (*Nature*, 1945, **155**, 479) suggested that puberulic acid might be a hydroxystipitatic acid but adduced no evidence to support this formulation; stipitatic acid itself was claimed by the same author (*ibid.*, p. 50) to be a derivative of tropolone (I). More recently McGowan (*Chem. and Ind.*, 1947, **66**, 205) advanced structures (II) and (III) for puberulic and puberulonic acid respectively, but again without experimental support.

In the present work, the two acids were isolated from the culture medium of *P. aurantio-virens* essentially as described by Birkinshaw and Raistrick (*loc. cit.*), although the yield was increased by using a relatively high temperature (30°) for the growth of the mould. The formula for puberulonic acid, $C_9H_4O_6$, put forward by earlier workers has been amended to $C_9H_4O_7$, the results of analyses being supported by the preparation of a *complex*, $C_9H_4O_7,C_5H_5N$, with pyridine, of a condensation *product*, $C_{15}H_9O_5N_3$, with *o*-phenylenediamine, and by experiments on the hydrolysis of the acid. When puberulonic acid is heated in dilute sulphuric acid solution, one

molecular equivalent of carbon dioxide is evolved and puberulic acid is obtained in quantitative yield:

$$C_8H_4O_7 + H_2O \longrightarrow C_7H_4O_4 + CO_2$$

Thus the relationship between the acids has been finally established.

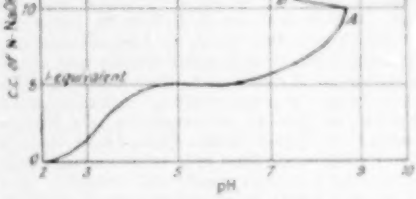


The potentiometric titration (Fig. 1) of puberulonic acid gives some support to the suggestion that a lactone grouping is present in the molecule, for during the neutralisation of the free acid a decrease in the pH was apparent on leaving the solution to stand or on further slow addition of small amounts of alkali at any point between about pH 7 and pH 10. An illustration of this effect is shown in Fig. 1.

Since in many respects puberulic acid has properties not unlike those of an aromatic compound, it seemed advisable to consider at the outset whether the evidence available supported a benzenoid formula. Birkinshaw and Raistrick (*loc. cit.*) and Barger and Dorrer (*loc. cit.*) had rejected the possibility that puberulic acid might be a dihydroxybenzenedicarboxylic acid because the decarboxylation product they obtained was not identical with any of the dihydroxybenzoic acids. Several pieces of evidence suggest that puberulic acid contains three aromatic hydroxyl groups; the dimethyl derivative formed on alkaline hydrolysis of "tetramethylpuberulic acid" gives a strong ferric reaction, and the *diacetyl* derivative of decarboxylated puberulic acid likewise gives an immediate coloration with ferric chloride. Furthermore, the isolation of a compound containing only one carbomethoxy-group from the hydrogenation product of the tetramethyl derivative suggests that puberulic acid itself contains only one carboxyl group. For these reasons structure (IV) for puberulic acid appeared worthy of consideration; on this basis the formulation of puberulonic acid as (V) might account for its condensation with *o*-phenylenediamine in the manner of an α-diketone, its yellow colour, and, if somewhat less readily, its conversion into puberulic acid on acid hydrolysis.

FIG. 1.

Potentiometric titration of puberulonic acid. The portion A—B of the curve shows the decrease in pH during slow addition of alkali.



The most serious objections to formulæ (IV) and (V) were that no carbonyl derivatives of either puberulic or decarboxylated puberulic acid could be prepared and that puberulonic acid could not be acetylated, but nevertheless it was felt that the hypothesis should be tested by comparison of decarboxylated puberulic acid with 2 : 3 : 5-*trihydroxybenzaldehyde*. This aldehyde had not been previously described and it has now been obtained in 20% overall yield by the Rosenmund reduction of 2 : 3 : 5-triacetoxybenzoyl chloride and subsequent hydrolysis of the 2 : 3 : 5-*triacetoxybenzaldehyde* produced. A comparison of the properties of 2 : 3 : 5-trihydroxybenzaldehyde and the decarboxylation product of puberulic acid shows that there is little resemblance between them (Table I). The ultra-violet absorption spectra of the two compounds are shown in Fig. 2, and those of puberulic and puberulonic acids in Fig. 3.

The other trihydroxybenzaldehydes have been described in the literature and all are different from the decarboxylation product of puberulic acid. The only possible benzenoid structures, $C_7H_6O_4$, which accommodate two phenolic groups and a carboxyl group are those of the

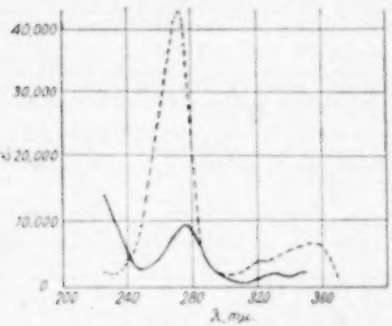
dihydroxybenzenedicarboxylic acids and the trihydroxyformylbenzoic acids (*e.g.*, IV); these structures have now been shown to be untenable for puberulic acid. Other ring structures must be considered and we have, therefore, taken up afresh degradative studies on both puberulic and puberulonic acids; the results will be presented in a separate communication.

TABLE I.

	2 : 3 : 5-Trihydroxybenzaldehyde.	Decarboxylated puberulic acid.
Colour	Canary yellow	Colourless
M. p.	187° (decomp.)	237—238°
2 : 4-Dinitrophenylhydrazone	Orange-red derivative	No reaction
Ferric reaction	Olive green	Deep blood-red
Condensation with ω-hydroxyacetophenone	Wine-red colour	No reaction
Coloration with aqueous sodium hydroxide	Golden-yellow	Light brown; rapidly darkens

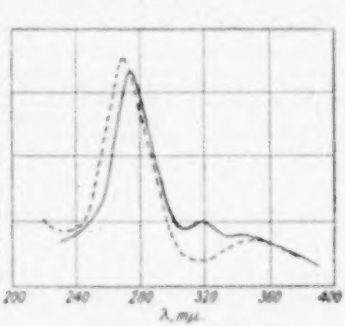
2 : 3 : 5-Trihydroxybenzaldehyde was also prepared, albeit in poor yield, by oxidation of α-resorcylaldehyde with potassium persulphate. There are several recorded examples of the

FIG. 2.



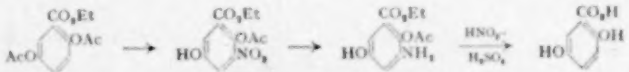
——— 2 : 3 : 5-*Trihydroxybenzaldehyde in ethanol.*
— — *Decarboxylated puberulic acid in ethanol.*

FIG. 3.



——— *Puberulonic acid in water.*
— — *Puberulic acid in water.*

preparation of aromatic hydroxyaldehydes by this reaction (*e.g.*, Baker and Brown, *J.*, **1948**, 2303) but this is the first instance in which it has been used to hydroxylate a dihydroxybenzaldehyde. The oxidation was carried out in an atmosphere of nitrogen and the product isolated by the method of Baker, Brown, and Scott (*J.*, **1939**, 1922). In connection with the synthesis of **2 : 3 : 5**-triacetoxybenzoyl chloride required for the preparation of the trihydroxybenzaldehyde, a number of routes to **2 : 3 : 5**-*trihydroxybenzoic acid* were investigated and it was eventually obtained in 15% yield by persulphate oxidation of α-resorcylic acid. The conditions for this oxidation were worked out in preliminary experiments on the oxidation of salicylic acid to gentisic acid (cf. Schering, D.R.-P. 81,297; Graebe and Martz, *Annalen*, 1905, **340**, 213; Nandor and Mauthner, *J. pr. Chem.*, 1940, **156**, 150) which was itself required for another possible route to **2 : 3 : 5**-trihydroxybenzoic acid via 3-amino-2-acetylgentisic acid. This latter compound, in



the form of its *ethyl* ester, was diazotised by the method of Hodgson and Walker (*J.*, **1933**, 1620), but heating the diazonium salt with 60% sulphuric acid under reflux gave gentisic acid (30%). This behaviour recalls that of aminogallic acid which under similar conditions is deaminated giving gallic acid (Power and Shedden, *J.*, 1902, **81**, 73). On the other hand 5-aminosalicylic acid was successfully converted into gentisic acid by this method.

Experimental.

Puberulic and Puberulonic Acid.—The acids were isolated from the culture medium of *Penicillium aurantio-virens* by a modification of the method of Birkinshaw and Raistrick (*loc. cit.*). The mould was grown at 30° rather than at 24—25° as previously recommended, thereby increasing the yield of the acid and decreasing the production of mould mycelium. After separation of the medium from the associated mycelial mat, and clarification of the solution by passage through a Sharples centrifuge, the pH was adjusted to 5·5 by the addition of sodium hydroxide solution. *N*-Nickel sulphate solution (900 c.c. for each 15 l. of mould solution) was then added, the pH again brought to 5·5, and the red nickel complex which separated was collected on the Sharples centrifuge. Decomposition of the nickel complex and separation of the mixed acids were carried out by the method of Barger and Dorrer (*loc. cit.*). From 20 l. of culture fluid 12 g. of mixed puberulic and puberulonic acid were obtained.

Puberulic acid (2 g.) was crystallised from methanol (50 c.c.), dissolution being effected in a hot extraction apparatus. The acid formed almost colourless plates, m. p. 318—320° (Found: C, 48·6; H, 3·0. Calc. for $C_9H_4O_4$: C, 48·2; H, 3·05%). The ultra-violet absorption of puberulic acid showed maxima at 2700 A. (ε, 35,200) and 3500 A. (ε, 7,160).

Puberulonic acid crystallised from ethyl malonate as fine yellow needles, m. p. 298° (decomp.) (Found: C, 48·0; H, 2·0. $C_9H_4O_5$ requires C, 48·2; H, 1·8. $C_9H_4O_6$ requires C, 49·0; H, 2·1%). Light absorption: Maxima at 2745 A. and 3170 A. (ε, 53,400 and 9,900 respectively). For the potentiometric titration of puberulonic acid, a well stirred suspension of the acid (1·12 g.) in water (20 c.c.) was neutralised with *N*-sodium hydroxide. The titration was followed potentiometrically by means of a calomel electrode-glass electrode system. The results are recorded in Fig. 1. The solution became pink at pH 7—8. This colour change was most marked after the addition of two equivalents of sodium hydroxide, and after the addition of three equivalents of alkali (pH 9·6) the solution remained orange in colour. No colour change was observed during the back-titration, and puberulonic acid was recovered unchanged from the acid solution. Barger and Dorrer (*loc. cit.*) claimed that the solution became colourless at pH 8—9.

Condensation of Puberulonic Acid with o-Phenylenediamine.—The acid (112 mg.) and *o*-phenylenediamine (90 mg.) were dissolved in just sufficient ethanol and heated under reflux for 4 hours, during which time a vermilion-red crystalline solid (125 mg.) separated. This *product* charred without melting on being heated to 350° and it was soluble with difficulty in water and organic solvents (Found: C, 60·6; H, 3·0; N, 9·3. $C_{15}H_8O_5N_2$ requires C, 60·8; H, 2·7; N, 9·4%).

Puberulonic Acid–Pyridine Complex.—Puberulonic acid (90 mg.) was heated with pyridine (2 c.c.) on a water-bath for 6 hours. Excess of pyridine was removed under reduced pressure, and the residual yellow solid was extracted with acetone to give relatively soluble unchanged puberulonic acid (10 mg.), leaving an insoluble *product* (70 mg.) which formed yellow needles, m. p. 257—258° (decomp.), from glacial acetic acid (Found: C, 55·5; H, 3·2; N, 4·6. $C_9H_4O_5,C_5H_5N$ requires C, 55·4; H, 3·0; N, 4·6%).

Conversion of Puberulonic Acid into Puberulic Acid.—A continuous stream of nitrogen, freed from carbon dioxide and oxygen, was passed through a boiling suspension of puberulonic acid (295 mg.) in 2*N*-sulphuric acid (50 c.c.). The carbon dioxide evolved in the reaction was collected quantitatively in barium hydroxide solution (90 c.c. of *N*/10) and after 8 hours the excess of barium hydroxide was determined by titration. Continuation of the hydrolysis for a further 2 hours did not change the titre (volume of barium hydroxide neutralised by carbon dioxide, 28 c.c.; calc. for 1 molar equivalent of carbon dioxide, 30 c.c.). The brown crystalline solid (243 mg.) formed in the course of reaction was separated and mixed with a further small quantity of solid (25 mg.) obtained by continuous ether extraction of the filtrate for 8 hours. The crude mixture, m. p. 305°, was repeatedly crystallised from acetone to give a faintly yellow micro-crystalline powder, m. p. 315° alone or mixed with an authentic specimen of puberulic acid (Found: C, 48·8; H, 3·2%).

Hydrogenation of Tetramethylpuberulic Acid (cf. Barger and Dorrer, *loc. cit.*).—Tetramethylpuberulic acid (534 mg.), m. p. 112°, was hydrogenated in pure glacial acetic acid at atmospheric temperature and pressure with a platinum catalyst. Six moles of hydrogen were absorbed and the solution was decolorised after the addition of 5 moles. The residue (500 mg.) obtained on removal of the acetic acid under reduced pressure was treated with water (5 c.c.), and the solution extracted with ether (2 × 10 c.c.). When the residual aqueous solution was treated with 2:4-dinitrophenylhydrazine a voluminous red precipitate separated. This precipitate was amorphous and oxidised in air; all attempts to purify it were unsuccessful. The ethereal extract was dried and evaporated, yielding a light-coloured oil (260 mg.) which on distillation gave a volatile fraction (160 mg.) and a residue which decomposed when further heated. The volatile fraction was redistilled; it had b. p. 120—125° 0·1 mm. and left only a trace of residue (Found: C, 59·7; H, 8·0; sap. val., 202, 204; active H (Zerewitinoff), 0·30%. $C_{14}H_{18}O_3(CO_2CH_3)_2$ requires C, 59·5; H, 8·0%; sap. val., 202; 1 active H, 0·49%).

Acetylation of Decarboxylated Puberulic Acid.—Decarboxylated puberulic acid (150 mg.) (Barger and Dorrer, *loc. cit.*), acetic anhydride (1·0 g.), and sodium acetate (0·6 g.) were heated under reflux at 140—150° for 30 minutes. The mixture was then diluted with water (20 c.c.) and acidified with hydrochloric acid. The clear solution was evaporated under reduced pressure at 25° and the residue extracted with ether. Removal of the solvent from the ethereal extract gave a brown resin which was distilled (110°/0·4 mm.) to give a light-yellow resin (70 mg.). The latter crystallised from ether–light petroleum (b. p. 40—60°) as colourless prisms, m. p. 124·5—125° (Found: C, 55·1; H, 4·4. $C_9H_4O_4(O{\cdot}CO{\cdot}CH_3)_2$ requires C, 55·4; H, 4·2%). The *diacetyl* derivative gave an immediate purple coloration with ferric chloride.

Gentisic Acid.—(*a*) *From salicylic acid.* Salicylic acid (18 g., 1 mol.) was dissolved in water (375 c.c.) containing sodium hydroxide (25 g., 5 mols.). The solution was brought to 35—40° and maintained at this temperature during the course of the experiment. Potassium persulphate (35 g., 1·1 mols.) was added portionwise during 3 hours. The reaction mixture, which rapidly developed a deep chocolate-brown colour, was left for 36 hours at room temperature and then acidified with concentrated hydrochloric acid until just acid to Congo-red. This solution was extracted with ether (3 × 300 c.c.), and the combined

ethereal extracts dried and evaporated to yield unchanged salicylic acid (9·5 g.). A further quantity of hydrochloric acid (100 c.c.) was added to the mother-liquors which were then kept at room temperature for 48 hours and extracted with ether (5 × 200 c.c.). The combined ethereal extracts were dried, clarified with charcoal, and evaporated, to yield crude gentisic acid (9·5 g.), m. p. 195—198°, usually of sufficient purity for conversion into the ester. Further purification was effected by recrystallisation of the crude acid from water (charcoal).

(b) *From 5-aminosalicylic acid.* 5-Aminosalicylic acid (Puxeddu, *Gazzetta*, 1929, **59**, 10) (4·3 g.) was dissolved in concentrated sulphuric acid (30 c.c.) and the solution cooled to below 10°. A solution of sodium nitrite (2·5 g.) in concentrated sulphuric acid (15 c.c.) was prepared by stirring the nitrite into the acid at 0° and completing dissolution by raising the temperature to 70°. After cooling to 5°, this solution was stirred into the sulphuric acid solution of 5-aminosalicylic acid, and the mixture added portionwise to glacial acetic acid (55 c.c.) during an hour, the temperature being kept below 20°. Anhydrous ether (50 c.c.) was then added, whereupon a fine white precipitate of sodium sulphate was obtained and after 3 hours at 0° this was removed (4·0 g.). A further quantity of ether (300 c.c.) was stirred into the mixture, and after 24 hours at 0° a large quantity of feathery crystals had separated which were shown to be the diazonium salt from 5-aminosalicylic acid. The crystalline solid was separated, and washed with 50% glacial acetic acid–ether (20 c.c.) and finally with ether (20 c.c.). The still moist crystals were dissolved in sulphuric acid (15 c.c. of 20%), and the solution added dropwise to boiling sulphuric acid (70 c.c. of 60%). After the mixture had been heated under gentle reflux for 45 minutes, evolution of nitrogen ceased and the solution was cooled and extracted with ether (5 × 100 c.c.). The dried ethereal extract was clarified with charcoal and evaporated to yield gentisic acid (2·1 g.), m. p. 196—198°.

2 : 3 : 5-*Trihydroxybenzoic Acid.*—The experimental procedure was similar to that described for gentisic acid. α-Resorcylic acid (32 g.) yielded unchanged starting material (12 g.) and crude 2 : 3 : 5-*trihydroxybenzoic acid* (10 g.). The crude acid was washed with ice-water and recrystallised repeatedly from water (charcoal) to give the pure acid (2·5 g.) as lemon-yellow needles, m. p. 223° (decomp.) (Found: C, 49·8; H, 3·6. $C_7H_6O_5$ requires C, 49·4; H, 3·5%). The acid gave a reddish-brown colour with ferric chloride.

2 : 3 : 5-*Triacetoxybenzoic Acid.*—2 : 3 : 5-Trihydroxybenzoic acid (7·2 g.), sodium acetate (15 g.), and acetic anhydride (30 c.c.) were heated initially at 85—90° until the acid dissolved, and then under reflux for 3 hours. The cooled solution was poured into water (150 c.c.), acidified with sulphuric acid (21 c.c. of 10*N*.), and extracted with ether (6 × 200 c.c.). After removal of the ether, the *triacetoxy-acid* remained as a white crystalline solid (11·4 g.) and after recrystallisation from benzene had m. p. 139—140° (Found: C, 53·1; H, 4·1. $C_{13}H_{12}O_8$ requires C, 52·7; H, 4·1%).

2 : 3 : 5-*Triacetoxybenzoyl Chloride.*—2 : 3 : 5-Triacetoxybenzoic acid (6·1 g.) and thionyl chloride (20 c.c.) were heated on a water-bath under reflux for 40 minutes, by which time evolution of sulphur dioxide had ceased. Removal of the excess of thionyl chloride *in vacuo* gave a gum which crystallised slowly in the ice-chest. The crystals were washed with light petroleum (b. p. 60—80°), and dried on porous tile and then in a vacuum-desiccator over phosphoric oxide. The product (6·3 g.) had m. p. 70—75°. Further purification could not be effected; attempted micro-distillation caused decomposition, and crystallisation could not be achieved from light petroleum, benzene, or xylene. With *p*-toluidine, the acid chloride gave 2 : 3 : 5-*trihydroxybenzo-p-toluidide*, which had m. p. 166—167° after recrystallisation from ethanol (Found: C, 62·7; H, 5·2; N, 3·7. $C_{20}H_{14}O_7N$ requires C, 62·3; H, 5·0; N, 3·6%).

2 : 3 : 5-*Triacetoxybenzaldehyde.*—2 : 3 : 5-Triacetoxybenzoyl chloride (5·5 g.), xylene (30 c.c.), and palladium–barium sulphate (2 g.; 2% of Pd) were placed in a 150-c.c. round-bottomed flask equipped with a reflux condenser, a sealed Hershberg stirrer, and a gas inlet tube reaching to the bottom of the flask. A brisk stream of hydrogen was passed through the rapidly stirred mixture, and the temperature raised to reflux. The exit gases were bubbled into water, and the evolved hydrogen chloride titrated from time to time. After 5 hours no more hydrogen chloride was formed, 85% of the theoretical amount having been collected. After cooling, catalyst was removed and washed thoroughly with dry ether (150 c.c.). The ether and xylene extracts were combined, washed with sodium hydrogen carbonate solution (50 c.c.) and then water (2 × 50 c.c.), and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the resinous residue crystallised partly on prolonged cooling. The crystals were washed with dry ether (10 c.c.) and recrystallised first from benzene and then from ether–light petroleum (b. p. 40—60°) or from benzene. The *product* (3·2 g.) had m. p. 90—91° (Found: C, 55·6; H, 4·6. $C_{13}H_{12}O_7$ requires C, 55·7; H, 4·3%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid (90%) in canary-yellow feathery needles, m. p. 240° (decomp.) (Found: C, 49·3; H, 3·6; N, 12·5. $C_{19}H_{16}O_{10}N_4$ requires C, 49·7; H, 3·3; N, 12·2%).

2 : 3 : 5-*Trihydroxybenzaldehyde.*—(a) *From* 2 : 3 : 5-*triacetoxybenzaldehyde.* The triacetoxy-aldehyde (1·2 g.) and anhydrous potassium acetate (4·8 g.) were dissolved in dry methanol (50 c.c.) and heated under reflux in a current of hydrogen for 2 hours. The cooled solution was acidified to Congo-red with sulphuric acid (30 c.c. of 2*N*.) and kept at 0° for 3 hours. Sodium sulphate was separated by filtration, and the filtrate extracted with ether (5 × 50 c.c.). The extract was dried and the solvent removed *in vacuo*, leaving a black tar. This was dried by distillation with benzene and again extracted with dry ether (100 c.c.). Removal of the ether gave a lemon-yellow solid (200 mg.) which was further purified by sublimation at 130°/10^{-2} mm., giving a yellow micro-crystalline solid, m. p. 187° (decomp.), alone or mixed with the product prepared by persulphate oxidation (see below).

(b) *From α-resorcylaldehyde.* α-Resorcylaldehyde (22·5 g., 1 mol.) was dissolved in aqueous sodium hydroxide (32·6 g. (5 mols.) in 450 c.c. of water) which had been freed from air by passing nitrogen through it for some time. The solution was warmed to 35—40° and maintained at this temperature during the course of the experiment. Potassium persulphate (48 g., 1·1 mols.) was added in portions during 3 hours, the reaction mixture rapidly becoming deep chocolate-brown. The mixture was set aside at room temperature for 36 hours, and then acidified with concentrated hydrochloric acid until just acid to Congo-red. The copious chocolate-coloured precipitate which separated was collected (18 g.); it was mainly unchanged starting material. The mother-liquors were extracted with ether

(3 × 300 c.c.), and the extract gave a further small amount of unchanged starting material. Concentrated hydrochloric acid (150 c.c.) and ether (300 c.c.) were added to the aqueous layer, and the mixture was heated under reflux on a water-bath at 70° for 1 hour. The ethereal layer was separated, dried, and clarified with charcoal. After removal of the solvent the dark-coloured residue was extracted with boiling benzene, and the benzene extract on cooling deposited a small amount of yellow crystalline material (20 mg.). Further extraction of the mother-liquors with chloroform (4 × 300 c.c.) and removal of the chloroform under reduced pressure gave a second crop of crude material (20 mg.). Purification by sublimation at 130°/10^{-4} mm. gave a yellow micro-crystalline solid which charred at 160° and decomposed at 187° (Found: C, 54·9; H, 4·0. $C_9H_6O_4$ requires C, 54·5; H, 3·0%).

The *aldehyde* gave an olive-green colour with ferric chloride and a wine-red colour (pyrylium salt) with *o*-hydroxyacetophenone under the conditions used in anthocyanin synthesis (*e.g.*, Robinson and Todd, *J.*, 1932, 2293). The 2 : 4-*dinitrophenylhydrazone*, m. p. >255° (decomp.), was very sparingly soluble in the common organic solvents (Found: N, 16·8. $C_{15}H_{10}O_7N_4$ requires N, 16·8%).

2-*Hydroxy*-3 : 5-*dimethoxybenzoic Acid*.—2 : 3 : 5-Trihydroxybenzoic acid (500 mg.) and methyl sulphate (6 c.c.) were stirred vigorously during dropwise addition of 5% potassium hydroxide solution. The addition was carried out at such a rate that the solution remained acid to litmus. A slight excess of potassium hydroxide solution was then added and the mixture heated at 70° for 1½ hours. The cooled mixture was acidified with 3*N*-hydrochloric acid and continuously extracted with ether for 6 hours. The ethereal extract was dried and then decolorised with charcoal, and the solvent removed *in vacuo*, yielding a brown solid. After two recrystallisations from water this gave colourless needles, m. p. 180·5° (Found: C, 54·7; H, 5·6. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%). The acid gave a deep greenish-blue ferric chloride reaction. This *acid* appeared to be identical with the hydroxydimethoxybenzoic acid obtained by Calam, Clutterbuck, Oxford, and Raistrick (*Biochem. J.*, 1947, **41**, 458) in the course of their degradation of methylated geodin.

Ethyl Diacetylgentisate.—Ethyl gentisate (21·5 g.; Jach, *Monatsh.*, 1905, **26**, 841) was dissolved in acetic anhydride (115 c.c.), concentrated sulphuric acid (2 c.c.) added, and the mixture set aside at room temperature for 36 hours. The solution was poured into ice–water (400 c.c.) and set aside in the ice-chest: the colourless oil which separated deposited crystals of the *diacetyl* ester (27·0 g.), which had m. p. 69·5° after recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 58·6; H, 5·2; *O*-Ac, 34·1. $C_{13}H_{14}O_6$ requires C, 58·7; H, 5·3; *O*-Ac, 32·3%).

Ethyl 3-*Nitro*-2-*acetylgentisate*.—Ethyl diacetylgentisate (14·8 g.) was added in small portions during 90 minutes to well-stirred fuming nitric acid (14·3 c.c.; *d* 1·5) maintained at 10—15° by ice-cooling. After addition was complete, the mixture was set aside for 40 minutes and the temperature allowed to rise to 20°. The mixture was then poured on crushed ice, whereupon the *nitro*-ester separated as an amorphous solid. Crystallisation from 50% ethanol (charcoal) yielded fine lemon-yellow needles (7·5 g.), m. p. 104·5° (Found: C, 49·3; H, 4·0; N, 5·3. $C_{11}H_{11}O_7N$ requires C, 49·0; H, 4·1; N, 5·2%).

Ethyl 3-*Amino*-2-*acetylgentisate*.—The foregoing nitro-ester (5 g.) was dissolved in methanol (300 c.c.) and hydrogenated using a Raney nickel catalyst (3 g.) at atmospheric pressure. The hydrogen uptake, which was slightly in excess of the calculated value for the hydrogenation of the nitro-group to an amino-group, was complete in 2 hours. After the wine-red solution had been decolorised with charcoal, methanol was removed *in vacuo* to yield the *amino*-ester (3·7 g.) as colourless plates, m. p. 139·5—140° after crystallisation from 80% methanol (Found: C, 55·4; H, 5·2; N, 6·0; *O*-Ac, 21·0. $C_{11}H_{13}O_5N$ requires C, 55·2; H, 5·4; N, 5·9; *O*-Ac, 18·0%).

Diazotisation and Hydrolysis of Ethyl 3-*Amino*-2-*acetylgentisate*.—The above amino-ester (1·25 g.), dissolved in glacial acetic acid (12·5 c.c.), was stirred into a mixture of sodium nitrite (0·6 g.) and concentrated sulphuric acid (6·5 c.c.), the temperature being kept below 15° by external cooling. The mixture was allowed to warm to room temperature, and after 30 minutes diazotisation was complete as shown by coupling tests with α-resorcylic acid. The solution was diluted with an equal volume of water and added dropwise to boiling sulphuric acid (50 c.c. of 60%) during 10 minutes. After cooling, the solution was continuously extracted with ether for 6 hours, and the ethereal extract dried and clarified with charcoal. Evaporation yielded crude gentisic acid (0·22 g.). Purified by sublimation it had m. p. 209° alone or mixed with an authentic specimen.

Grateful acknowledgment is made to the Royal Commissioners for the Exhibition of 1851 for a Senior Studentship awarded to C. H. H., to the University of New Zealand for a Schirtcliffe Research Scholarship and to the Council of Scientific and Industrial Research of New Zealand for grants to R. E. C., and to Roche Products Ltd. for generous assistance in the growing of mould material.

University Chemical Laboratory, Cambridge. [*Received, July 26th*, 1949.]

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2. *Puberulic and Puberulonic Acids. Part II. Structure.*

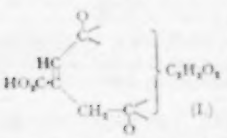
By R. E. Corbett, A. W. Johnson, and A. R. Todd.

Oxidation of puberulic acid with alkaline hydrogen peroxide yields aconitic acid. On the basis of this and other evidence, puberulic acid is formulated as 6 : 7-dihydroxytropolone-4-carboxylic acid (II), or one of its tautomeric forms. The properties of puberulonic acid, in particular its ready conversion into (II) in boiling aqueous solution, indicate that it has structure (VI), although a final decision between this and an isomeric structure containing a γ- rather than a δ-lactone grouping cannot yet be made.

Preliminary work on the structure of the mould products puberulic and puberulonic acids (Birkinshaw and Raistrick, *Biochem. J.*, 1932, **26**, 441; Barger and Dorrer, *ibid.*, 1934, **28**, 11)

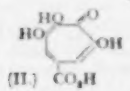
suggested that they had the molecular formulæ $C_8H_6O_8$ and $C_9H_6O_8$ respectively, but in Part I of this series (preceding paper) we amended the formula of puberulonic acid to $C_8H_6O_7$. The properties of puberulic acid as outlined in the previous paper indicate that it contains a carboxyl and three enolic groupings, but no direct evidence has been obtained for the presence of a free carbonyl group. It is apparent that the puberulic acid molecule must contain therefore the equivalent of five double bonds if the remaining oxygen atom is present as an ether linkage, or four double bonds if it is present as a masked carbonyl group. The nature of the ultra-violet absorption spectrum (preceding paper) and the facts that puberulic acid neither absorbs bromine from an acetic acid solution nor forms an adduct with maleic anhydride eliminate possible open-chain structures. In any case, the accommodation of at least four double bonds in an open chain of seven carbon atoms (allowing for the carboxyl group) would require the presence of acetylenic or cumulative ethylenic linkages.

Important evidence on the nature of the cyclic system present in puberulic acid has been gained from oxidative degradation. Except for carbon dioxide, no identified products had been previously obtained from the oxidation of puberulic acid with, *e.g.*, permanganate, chromic acid, neutral hydrogen peroxide, alkaline hydrogen peroxide, or iodine and potassium hydroxide (Barger and Dorrer, *loc. cit.*). We have repeated the oxidation with alkaline hydrogen peroxide and have obtained aconitic acid in 40% yield; the identity of this product has been confirmed by direct comparison with an authentic specimen and by its hydrogenation to tricarballylic acid. On the other hand, oxidation with nitric acid gave only oxalic acid (1 mole) and carbon dioxide, and ozonolysis gave carbon dioxide (5·2 moles) with a small amount of an unidentified non-volatile acidic residue. This formation of aconitic acid establishes the relative positions of six of the eight carbon atoms of puberulic acid, and the molecule may now be represented as (I): A six-membered ring in puberulic acid would necessarily be benzenoid, and benzenoid structures have already been shown to be untenable (preceding paper). Thus, if the acid is monocyclic, there must be present either a five-membered or a seven-membered ring, and, since structures based on these systems could not accommodate the equivalent of four double bonds, the unplaced oxygen must be embodied in an inert carbonyl group rather than in an ether linkage. This argument also eliminates structures containing an oxygen-heterocyclic ring. A further theoretical possibility would be a formula based on the *bicyclo* 0 : 1 : 4-heptane system, but no reasonable structures can be devised which are derived either from this bicyclic system or from a monocyclic five-membered ring and at the same time account for the formation of aconitic acid by oxidation. Of seven-membered ring structures based on (I), the only possibility is (II) (or one of its tautomeric forms), according to which the acid is formulated as a derivative of *cyclo*-heptatrienolone (tropolone) (III).



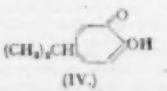
The occurrence of tropolone derivatives in Nature is now well established, *e.g.*, the thujaplicins (Erdtman *et al.*, *Nature*, 1948, **161**, 719; *Acta Chem. Scand.*, 1948, **2**, 625, 639, 644), colchicine (Dewar, *Nature*, 1945, **155**, 141, 479; Arnstein *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1669; Lettré, *Angew. Chem.*, 1947, **59**, *A*, 218), and purpurogallin (Barltrop and Nicholson, *J.*, 1948, 116; Haworth, Moore, and Pauson, *ibid.*, p. 1045) which occurs as its glucoside, eriophyesin. There is also evidence that stipitatic acid, a mould product of *Penicillium stipitatum* (Birkinshaw, Chambers, and Raistrick, *Biochem. J.*, 1942, **36**, 242), is a hydroxytropolonecarboxylic acid (Dewar, *Nature*, 1945, **155**, 50; Corbett, Johnson, and Todd, unpublished work), and indeed Dewar (*loc. cit.*) has suggested, although without any experimental evidence, that puberulic acid might be a hydroxystipitatic acid.

Characteristic features of the various tropolones hitherto examined have been (i) the inert carbonyl group which gives no characteristic reactions, (ii) the formation of substitution rather than addition products with bromine, and (iii) the formation of benzenoid derivatives containing one extra carboxy-group on fusion with potassium hydroxide. Reactions (i) and (ii) are shown



(II.)

(III.)



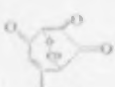
(IV.)

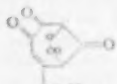
(V.)

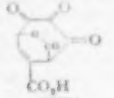
by puberulic acid, but the potassium hydroxide fusion has so far failed to yield an aromatic product. The acid is unchanged by potassium hydroxide below 320°; above this temperature,

gas is evolved and considerable charring occurs, but no recognisable product has been isolated. In this connection, it is interesting to note that, whereas γ-thujaplicin (IV) was converted with potassium hydroxide into *p*-isopropylbenzoic acid at 230° (Erdtman *et al.*, *loc. cit.*), and benztropolone (V) into α-naphthoic acid at 185° (Cook and Somerville, *Nature*, 1949, **163**, 410), stipitatic acid, a monohydroxytropolone derivative, required to be heated to 300° to give 5-hydroxyisophthalic acid (Birkinshaw, Chambers, and Raistrick, *loc. cit.*), so that the relative stability of puberulic acid, a dihydroxytropolone derivative, towards potassium hydroxide is not unexpected.

Perhaps the most interesting aspect of the structure (II) for puberulic acid is the manner in which it explains the relationship between puberulic and puberulonic acids. We have shown (*loc. cit.*) that puberulonic acid, on being heated with dilute sulphuric acid under reflux, is converted into puberulic acid with evolution of carbon dioxide: $C_9H_4O_5 + H_2O \longrightarrow C_8H_6O_4 + CO_2$. It is now found that this change occurs even on heating the acid with water at 100° and thus there is a strong suggestion of the presence of a potential β-keto-acid structure in puberulonic acid. We have also previously demonstrated the existence of α-diketone and lactone groupings and we now propose structure (VI) for puberulonic acid in order to accommodate all these features:


(VI.)


(VII.)


(VIII.)

It will be evident that hydrolysis of the lactone group in (VI) gives a β-keto-acid which, on loss of carbon dioxide, passes into a ketonic form of puberulic acid. Structure (VI) also accounts for the α-diketonic properties of puberulonic acid and hence its yellow colour, as well as for the fact that it cannot be acetylated.

Other possible formulæ for puberulonic acid are (VII) and (VIII), if we exclude structures containing a double bond at a bridgehead. Structure (VII) contains a γ-lactone grouping and there is no decisive evidence available at present to distinguish between it and (VI). Whereas the ready opening of the lactone ring on heating the acid with water and the fact that the quinoxaline derivative of puberulonic acid does not evolve carbon dioxide when heated with dilute aqueous methanolic hydrochloric acid tend to favour the δ-lactone structure, the recovery of puberulonic acid on acidification of a solution of the sodium salt is perhaps more indicative of a γ-lactone formula.

The 1 : 2 : 3-triketone structure (VIII) is perhaps less likely, since such a compound would be expected to exist in a hydrated form and exhibit strong reducing properties. Further work is necessary, however, to decide between structures (VI) and (VII).

Experimental.

Conversion of Puberulonic Acid into Puberulic Acid.—A continuous stream of nitrogen, freed from carbon dioxide and oxygen, was passed through a boiling suspension of puberulonic acid (224 mg.) in water (25 c.c.). The carbon dioxide evolved in the reaction was collected quantitatively in barium hydroxide solution (98·8 c.c. of 0·1923*N*.), and at the end of 8 hours the excess of barium hydroxide was determined by titration (volume of barium hydroxide neutralised by carbon dioxide, 9·5 c.c.; calc. for 1 molar equivalent of carbon dioxide, 10·4 c.c.). The yellow crystalline solid (170 mg.) formed in the course of the reaction was separated and mixed with a further small quantity of solid obtained by continuous extraction of the filtrate for 8 hours. The crude mixture, m. p. 308°, was recrystallised from methanol to give a faintly yellow micro-crystalline powder, m. p. 311°, alone or mixed with an authentic specimen of puberulic acid.

Fusion of Puberulic Acid with Potassium Hydroxide.—Puberulic acid (200 mg.), water (0·5 c.c.), and potassium hydroxide (1 g.) were heated in a salt-bath at 240° and a further quantity of potassium hydroxide (1 g.) was added to increase the fluidity. The bath temperature was slowly raised to 300°, the melt remaining yellow and frothing considerably. After 10 minutes at 300—320°, the melt was cooled, dissolved in water (8 c.c.), and acidified with 3*N*-hydrochloric acid (12 c.c.) which caused vigorous evolution of gas. The copious precipitate was allowed to settle at 0° overnight, then separated, and dried (117 mg.), m. p. 300°. Mixed with an authentic specimen of puberulic acid, the product had m. p. 310°. The ferric chloride reaction of the material was identical with that of puberulic acid. The filtrate was evaporated to dryness at 50°/13 mm., and the solid residue remaining was continuously extracted with dry ether. Evaporation of the ether failed to yield any residue.

Repetition of the above experiment at a higher temperature, 320—340°, for 20 minutes caused extensive charring and yielded on acidification a deep reddish-brown mass that had m. p. >350° and was not identified.

Oxidation of Puberulic Acid with Hydrogen Peroxide.—Puberulic acid (500 mg.) was dissolved in N-sodium hydroxide (11 c.c.), hydrogen peroxide (4·9 c.c. of 31%) added, and the mixture set aside for 72 hours at room temperature, whereupon the solution changed from orange-red to colourless. The colourless solution was acidified with N-hydrochloric acid (12 c.c.) (evolution of carbon dioxide), and the mixture evaporated at 50°/13 mm. The colourless, rather gummy residue was continuously extracted with dry ether for 9 hours and gave, after removal of the ether *in vacuo*, a white solid contaminated with a trace of colourless resin. Purification was effected by repeated recrystallisation from dry ether–light petroleum (b. p. 40—60°) and finally by recrystallisation from 2*N*-hydrochloric acid. The purified product formed small white prisms, m. p. 187—189° (decomp.), which had m. p. 186—187° (decomp.) when mixed with authentic aconitic acid (m. p. 186—187°) (Found: C, 41·8; H, 3·5%; equiv. (titration), 59·4, 86. Calc. for $C_6H_6O_6$: C, 41·4; H, 3·5%; equiv., 58).

The above degradation product gave, under the conditions of the fluorescein reaction with resorcinol–sulphuric acid, a red solution with a pale greenish-yellow fluorescence in daylight and a beautiful sky-blue fluorescence in ultra-violet light, identical with that observed using authentic aconitic acid. With pyridine and acetic anhydride it showed the same series of colour changes as authentic aconitic acid.

Reduction of the Hydrogen Peroxide Oxidation Product.—The hydrogen peroxide oxidation product (116 mg.) was dissolved in methanol (25 c.c.) and hydrogenated at atmospheric pressure using Adams's platinum oxide catalyst. The hydrogen uptake was slightly in excess of that calculated for one double bond and was complete in 1 hour. The methanol was removed *in vacuo*, leaving an oil which solidified when kept for 24 hours at 0°. Recrystallisation from acetone (charcoal) yielded tricarballylic acid (50 mg.), m. p. 157—158°; mixed with authentic tricarballylic acid (m. p. 162—163°) it had m. p. 158—160°. Confirmation of the identity was provided by the fluorescein test: the colour observed corresponded precisely with that shown by an authentic specimen.

Nitric Acid Oxidation of Puberulic Acid.—Puberulic acid (50 mg.) was heated with distilled nitric acid (2 c.c.) at 100° for 2 hours. Copious brown fumes were evolved and the mixture rapidly changed from red to pale brown. It was evaporated to dryness at 100°, and water (2 c.c.) added to the residue, which was again taken to dryness. This process was repeated three times, the last trace of volatile material being removed *in vacuo*, leaving a colourless solid residue (20 mg.). This residue gave no colour reaction with ferric chloride but a blue colour with diphenylamine, and decolorised potassium permanganate when gently warmed. Purification was effected by sublimation at 80—90°/2×10^{-2} mm. and yielded oxalic acid (16·7 mg.), m. p. 187—188°, showing no depression on admixture with an authentic specimen of oxalic acid.

Ozonolysis of Puberulic Acid.—Ozonized oxygen was passed through a suspension of puberulic acid (198 mg.) in water (50 c.c.) and then through standard barium hydroxide until dissolution of the acid was complete (3 days). Carbon dioxide equivalent to 5·2 mols. per mol. of puberulic acid was evolved. The titratable acidity of the clear solution was initially 20 c.c. of 0·1*N*-alkali and decreased to 7·15 c.c. of 0·1*N*-alkali after ozonisation. Steam-distillation of the residue showed that none of the titratable acidity was due to volatile acids, nor did the distillate give any reaction with Brady's reagent. Evaporation of the ozonized solution gave a small amount of an acidic gum (10 mg.) which gave no characteristic colour reactions and was not further investigated.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, July 26th*, 1949.]

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3. *Ketonic Products of the Oxidation of the* cis- *and* trans-*Forms of Ricinoleic Acid.*

(Considered in relation with the author's work on the autoxidation of the unsaturated fatty acids.)

By GEORGE W. ELLIS.

The hitherto unknown cis-11-*keto*heptadec-8-*ene*-1-*carboxylic acid* (*λ-keto-oleic acid*) and its trans-*isomer* (*λ-ketoelaidic acid*) have been prepared by the chromic acid oxidation of ricinoleic and ricinelaidic acid, respectively. Both of these acids containing $\beta\gamma$-olefinic ketone grouping have been transformed, through their common hydrogen bromide additive product, 9-*bromo*-11-*keto*heptadecane-1-*carboxylic acid* (*ω-bromo-λ-ketostearic acid*), into the *trans*-form of their $\alpha\beta$-isomer, trans-11-*keto*heptadec-9-*ene*-1-*carboxylic acid*. Some of the properties of these compounds have been studied, particularly the quantitative nature of their alkaline hydrolyses. Their reactions with semicarbazide have been studied and special interest attaches to formation, from λ-keto-oleic acid, of a peroxide simultaneously with an *epoxy*-derivative.

THE main purpose of these investigations was to throw further light on the formation of unsaturated ketone groups during the autoxidation of the mono-unsaturated fatty acids. The products obtained from oleic and elaidic acid, after an oxygen uptake at 60—70° of about 20% by weight, contained only a low concentration of these unsaturated keto-acids, but contained substances regarded as resulting therefrom, such as elaidic acid oxide (m. p. 55·5°) in nearly 40% yield with its monoacyl derivatives, and oily, resinous polymers. The amount of

these substances became inappreciable when it was found possible to bring about autoxidation at 45—50°. In their place appeared β- and κ-keto-oleic acids, or their *trans*-isomers, as the main autoxidation products (Ellis, *Biochem. J.*, 1936, **30**, 753; 1950, in the press).

The existence of different isomers of these keto-acids and the appreciable chain degradation found to accompany autoxidation led to the formation of a complex mixture of these bodies from which no pure product can, with certainty, be regarded as having been isolated. The present study of similar compounds, obtained in a pure form from ricinoleic and ricinelaidic acids, confirms the evidence for the presence of the unsaturated ketonic acids as significant autoxidation products of the mono-unsaturated fatty acids; similar ketone formation has been observed for 1-methylcyclohexene (Dupont, *Bull. Soc. chim. Belg.*, 1936, **45**, 57; 1937, **46**, 21; Cook, *J.*, 1938, 1778). It was realised that carefully controlled oxidation of ricinoleic and ricinelaidic acids should afford acids containing βγ-unsaturated ketone groupings in *cis*- and *trans*-forms which by the catalytic action of acids and alkalis might undergo tautomeric change to the respective αβ-forms (cf. Kon *et al.*, *J.*, 1923, 1361 etc.; 1926, 2128). However, the *trans*-αβ-form was obtained from both the *cis*- and the *trans*-βγ-form by way of the hydrobromic acid additive product of the latter (cf. Blaise, *Bull. Soc. chim.*, 1905, **33**, 40).

λ-*Keto-oleic*, m. p. 39°, and -*elaidic acid*, m. p. 73°, have now been prepared by the oxidation of ricinoleic and ricinelaidic acid, respectively, with chromic acid below 15°. Both keto-acids have iodine values lower than the theoretical and, although the latter acid is perfectly stable, the former rapidly autoxidises in air, even at 0°. At room temperatures λ-keto-oleic acid absorbs 3—4 atoms of oxygen with evolution of carbon dioxide, to form a semi-solid mass containing up to 12·5% of a peroxide (calculated as a peroxide of keto-oleic acid with one active oxygen atom), an appreciable proportion of λ-*ketoperystearic acid*, m. p. 112·5° (2 : 4-*dinitrophenylhydrazone*, m. p. 119°), and oily substances giving reactions pointing to β-keto-acid formation. The instability of the unsaturated ketones has usually been attributed to polymerisation rather than to autoxidation, but explosive products have sometimes been observed (Eccott and Linstead, *J.*, 1930, 905), suggestive of the peroxide formation observed in the present studies.

In the present study of the autoxidation of oleic and elaidic acid, small and not greatly varying amounts of peroxides were formed at temperatures between 45° and 100°. At the lower temperatures high yields of the unsaturated keto-acids were obtained, with little evidence of their decomposition into the coloured, resinous oils which form the greater part of the products at higher temperatures. At all temperatures within the range, elaidic acid oxide, m. p. 55·5°, was also formed from both oleic and elaidic acid (maximum yield at 60—70°), with a copious evolution of carbon dioxide and water. Some of the oily fractions isolated gave marked enol reactions and yielded carbon dioxide on hydrolysis, so that β-keto-acid formation is probable. The products are thus closely comparable with those obtained by autoxidation of the olefinic keto-acid studied in the course of this work, and since, for the autoxidation of oleic and elaidic acid, a preliminary formation of olefinic keto-acids has been demonstrated in the author's contemporary work (Ellis, 1950, *loc. cit.*), it seems likely that for this process there is a sequence : olefinic acid ⟶ olefinic keto-acid ⟶ olefinic keto-acid peroxide ⟶ peroxidation products, including an epoxide, carbon dioxide, and water with other chain-peroxidation products.

λ-Keto-oleic and -elaidic acid absorb hydrogen bromide in dry carbon tetrachloride solution (cf. Blaise, *Bull. Soc. chim.*, 1905, **33**, 40; Eccott and Linstead, *loc. cit.*) to form the same ι-*bromo*-λ-*ketostearic acid*, m. p. 68°, in good yield. This is converted by aqueous potassium hydrogen carbonate at 100° into 11-*ketoheptadec*-9-*ene*-1-*carboxylic acid*, m. p. 50°, containing an αβ-unsaturated keto-group and considered to be the *trans*-form by analogy with the findings of the authors mentioned above.

Alkaline hydrolysis of λ-keto-oleic and -elaidic acid afforded a 40% yield (theory 43%) of hexyl methyl ketone, the isolation of which was facilitated by the use of a simple still-head (Ellis, 1950, *loc. cit.*). The other hydrolysis product, the semialdehyde of sebacic acid, was not isolated : it appeared to have polymerised under the action of the alkali. Since methyl hexyl ketone was obtained in very similar yields by alkaline hydrolysis of both the *cis*- and the *trans*-form of the βγ-isomers and from the *trans*-form of the αβ-isomer, it seems probable that the first two acids isomerise under the influence of alkalis (cf., *e.g.*, Eccott and Linstead, *loc. cit.*).

Condensed with phenylhydrazine and then treated with sulphuric–nitrous acid, all these olefine-ketonic acids gave an intense purple pyrazoline dye. This reaction was previously regarded as specific for αβ-olefinic ketones. It is a marked reaction of the oily products

obtained by the autoxidation of the mono-unsaturated fatty acids and is given by a linseed oil film which has been exposed to the air for a few hours at room temperatures.

Experimental.

λ-Keto-oleic (cis-11-*Ketoheptadec-8-ene-1-carboxylic*) *Acid from Ricinoleic Acid.*—A solution of recently prepared ricinoleic acid (80 g.) in acetic acid (500 ml.) was cooled with occasional stirring so as to crystallise a large proportion of the acetic acid without causing the mass to set and so hinder the next operation. Chromium trioxide (14 g.) in a minimum of water and acetic acid (100 ml.) was added with vigorous stirring, and the mixture was set aside for 2 hours at room temperature. It was then mixed with half its bulk of powdered ice, and the solid product was allowed to separate over a clear lower layer. The solid (which should contain a large proportion of ice) was washed by suction with ice-cold water until colourless. It crystallised from 80% ethanol at 0° in long, thin plates (10 g.), m. p. 39° (Found: C, 72·9; H, 10·7%; I.V., 56. $C_{18}H_{32}O_3$ requires C, 72·9; H, 10·9%; I.V., 85·7).

λ-Keto-oleic acid is very soluble in all the common organic solvents and crystallises well from light petroleum. Filtration of its solution in this solvent serves to remove possible traces of the epoxide described below. This acid is very unstable in air, absorbing oxygen to form a peroxide and other substances (see below). Although it clearly reacts with semicarbazide and with 2 : 4-dinitrophenylhydrazine, no pure derivatives have been isolated. It gives the following sensitive test: About 1 mg. is heated for a few seconds with an equal bulk of phenylhydrazine on a slide and the cold product is rubbed into a smear with a small drop of sulphuric acid. A few crystals of sodium nitrite are allowed to react completely with a drop of sulphuric acid. On causing these two smears to run together, an intense bluish-violet mass is obtained.

When boiled with water or diluted sulphuric acid, or when heated alone at 100° for an hour, λ-keto-oleic acid gives a yellow oil.

Alkaline Hydrolysis of λ-Keto-oleic Acid.—Slow distillation of this acid with 0·03*N*-sodium hydroxide in the apparatus referred to above, gave a 40% yield of methyl hexyl ketone (semicarbazone, m. p. and mixed m. p. 121°), but the yields fell off with an increased concentration of alkali:

Wt. taken, g.	Alkali.	Methyl hexyl ketone, g.	Yield, %.	Yield, %, corr.
0·2689	0·03*N*-NaOH	0·0960	36	40
0·1738	0·05*N*-NaOH	0·0535	31	34
0·2087	*N*-NaOH	0·0500	24	26
0·1510	10% KOH	0·0325	22	24
0·1958	10% K_2CO_3	0·0407	21	23

A blank experiment with pure methyl hexyl ketone in the same apparatus gave a 90% recovery, and the yields have been corrected accordingly, as shown in the last column. With the more concentrated alkali the hydrolytic reaction appears to be replaced in part by polymerisation. Acidification of the products remaining after distillation of the methyl hexyl ketone resulting from the less concentrated alkaline hydrolyses gave, apparently, polymers of sebacic acid semialdehyde as semi-solid oils (Found: equiv., 186. Calc. for $(C_{10}H_{18}O_3)_n$: equiv., 186). This equivalent rose to 240—260 when more concentrated alkali was employed, furnishing some evidence that the lower yield of methyl hexyl ketone was caused by polymerisation of the olefinic keto-acid. No Schiff's or other aldehydic reaction could be obtained, either before or after boiling these oils with dilute sulphuric acid, nor could any sebacic acid be detected after their oxidation with potassium permanganate. In such respects these sticky oils bear a close analogy with the polymerised product which King (*J.*, 1938, 1826) obtained by the action of alkali on azelaic acid semialdehyde.

λ-Keto-elaidic (trans-11-*Ketoheptadec-8-ene-1-carboxylic*) *Acid.*—Ricinelaidic acid, m. p. 52°, was prepared by exposing a layer of ricinoleic acid to nitrous fumes for about 2 days and purifying the product with dilute ethanol. This was oxidised with chromic acid in acetic acid in the manner described above. The crude product, however, was crystallised from 90% ethanol at room temperatures, unchanged ricinelaidic acid being retained in the mother-liquors. *λ-Keto-elaidic acid* (30%) crystallised from ethanol in rhombic and hexagonal plates, m. p. 73° (Found: C, 72·9; H, 10·8%; I.V., 68), and gave a *semicarbazone*, m. p. 94° (Found: N, 12·0. $C_{19}H_{35}O_3N_3$ requires N, 11·9%). The keto-acid was stable in air (during some months) and gave the pyrazoline test. It also gave a reddish-orange colour when treated with the phenylhydrazine and sulphuric acid alone. It was much more stable towards heat than was the *cis*-isomer, suffering only slight change during 2 hours at 100°, and afforded, though more slowly than its isomer, a 41% yield of methyl hexyl ketone on hydrolysis with 0·05*N*-sodium hydroxide.

9-*Bromo*-11-*ketoheptadecane*-1-*carboxylic Acid.*—λ-Keto-oleic (or elaidic) acid (1 g.) in carbon tetrachloride (10 ml.) was saturated with hydrogen bromide and the corked vessel was left in a cool place. The 9-*bromo*-11-*ketoheptadecane*-1-*carboxylic acid* which separated was crystallised from a filtered, light petroleum solution and then from carbon tetrachloride or 90% ethanol. It formed rods with pointed ends, often appearing as plate-like bundles (1·1 g.), m. p. 68° (Found: C, 57·2; H, 8·6; Br, 22·2. $C_{18}H_{33}O_3Br$ requires C, 57·3; H, 8·8; Br, 21·2%).

trans-11-*Ketoheptadec-9-ene-1-carboxylic Acid.*—The bromo-keto-acid was heated for 2 hours at 100° with 10% aqueous potassium hydrogen carbonate. After acidification the solution was extracted with light petroleum, and the residue left on evaporation of the solvent was crystallised successively from carbon tetrachloride (norite) and from ethanol. trans-11-*Ketoheptadec-9-ene-1-carboxylic acid* crystallised in well-defined hexagonal plates, m. p. 50° (Found: equiv., 297; I.V., 24. $C_{18}H_{32}O_3$ requires equiv., 296; I.V., 85·7). A low iodine value has been observed for αβ-olefinic ketones (Ecott and Linstead, *loc. cit.*). The acid gave a marked pyrazoline colour reaction, and with sulphurous acid gave a stable

cid. Hydrolysis of the acid with 0·05*N*-sodium hydroxide gave a 32·5% yield of methyl hexyl ketone. Autoxidation of this α*β*-isomer is under investigation.

Autoxidation of λ-Keto-oleic Acid.—(*a*) Specimens of λ-keto-oleic acid, left in loosely corked tubes for several months, became sticky and did not melt completely below 100°. The peroxide values ranged from 4·3 to 12·5% (calc. as a peroxide of the original acid). Extraction of the tube contents with light petroleum gave an unstable oily product of 17% peroxide content, which resisted further purification. The solid left after the extraction with light petroleum was extracted with acetone, and the solution filtered and evaporated. The residue in ethanol yielded an epoxide in the form of well-defined hexgonal plates of *λ-ketoepoxystearic* (11-*keto*-8 : 9-*epoxyheptadecane*-1-*carboxylic*) *acid*, m. p. 112·5° (Found: C, 69·1; H, 10·1; equiv., 311; *M* (Rast), 336; I.V., 5. $C_{18}H_{32}O_4$ requires C, 69·2; H, 10·3%; equiv. = *M*, 312). The 2 : 4-*dinitrophenylhydrazone* crystallised in plates, m. p. 119° (Found: N, 11·0. $C_{24}H_{36}O_7N_4$ requires N, 11·4%). Attempts to prepare a semicarbazone yielded an impure, yellow, amorphous *substance*, m. p. 201°, nearly insoluble in ethanol (Found: N, 18·2. $C_{19}H_{31}O_4N_3$ requires N, 11·4%).

This keto-epoxy-acid was also isolated in small amount as a by-product in the preparation of λ-keto-elaidic acid described above, and was detected in smaller amounts in the mother-liquors from λ-keto-oleic acid preparations. It was isolated by means of its sparing solubility in lukewarm light petroleum. When prepared from these sources this compound may have acquired its epoxy-group by autoxidation of the ricinoleic acid used for the chromic acid oxidations.

(*b*) λ-Keto-oleic acid (0·0576 g.) was dispersed on a small, opened roll of filter paper (36 sq. cm.), placed in the upper part of a test-tube containing a little saturated aqueous barium hydroxide at the base. The air was replaced by oxygen and the tube connected with a manometer and a source of oxygen. After 55 days, at room temperatures, 6·84 ml. (17% by wt.) of oxygen had been absorbed, corresponding to the addition of 3·33 atoms of oxygen. Acidification of the alkaline solution gave 0·49 ml. of carbon dioxide. The ratio of oxygen evolved as carbon dioxide to the total oxygen uptake was 0·07 as compared with ratios of 0·2—0·4 found for the autoxidation of monounsaturated fatty acids (Ellis, *loc. cit.*).

Extraction of the main autoxidation products from the filter paper with peroxide-free ether furnished a semi-solid material containing crystals of the λ-ketoepoxystearic acid and 15% of peroxide.

(*c*) λ-Keto-oleic acid was autoxidised in air in the form of a thin film on a glass plate at 42°. After 24 hours, extraction with *n*-hexane gave an oil containing 27% of peroxide. A solid fraction, insoluble in the cold solvent, was identified as the ketoepoxystearic acid.

The oily products of the above autoxidations gave enol reactions, which were not given by any of the olefinic keto-acids. These oils also yielded small quantities of sodium carbonate when hydrolysed by sodium hydroxide. The presence of *β*-keto-acids in these autoxidation products was therefore indicated.

Pyrazoline Test.—The purple colour obtained in the tests described above was also given by the oils from the autoxidation of the monounsaturated fatty acids and by linseed oil which had been exposed to the air for a day, or for a few hours in warm weather. A film of linseed oil so treated gives with concentrated sulphuric acid a deep brown colour, masking the bluish-purple colour of the test, which was, therefore, slightly modified in this case. The autoxidised film (about 1 mg.) was mixed with phenylhydrazine (about 2 mg.). The application of very little heat sufficed to bring about a vigorous reaction. The resulting mass was taken up in a few drops of chloroform and the solution dropped on the sulphuric and nitrous acid mixture. Intense blue or purple colours were obtained in this way.

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4. *The Seed Fat of* Parinarium laurinum. *Part I. Component Acids of the Seed Fat.*

By J. P. Riley.

The component acids of the seed oil of *Parinarium laurinum* have been examined and shown to contain besides parinaric acid, reported by earlier workers, substantial amounts of α-elaeostearic and oleic acids, together with minor proportions of palmitic, stearic, linoleic, and conjugated octadecadienoic acids. The identities of the unsaturated acids have been established by oxidation or bromination. Spectrographic values are presented for the determination of parinaric acid in oils, and for its behaviour to alkali isomerisation under the conditions used for the analysis of oils containing α-elaeostearic and linoleic acids. The mean composition of the component mixed fatty acids of two samples of oil from seeds collected in the Fiji Islands has been shown by low temperature crystallisation and spectrographic methods to be: palmitic 4, stearic 1, oleic 7·5, linoleic 2, conjugated octadecadienoic 1·5, α-elaeostearic 30·5, and parinaric acid 53·5% (wt.).

Parinarium laurinum, belonging to the family Rosaceæ, is a tree of moderate size, about 3 feet in girth and 30 feet high. It grows in Papua and New Guinea, Java, Borneo, and prolifically on the sea front and river valleys of the Fiji Islands. The tree bears ovoid fruit resembling potatoes and varying considerably in size; these are greatly valued by the natives for medicinal

and other purposes, and are known by a number of native names, the principal of which are Makita (Fiji) and Kusta (New Guinea).

The fruit itself consists of a light-brown, very fibrous shell about ¼" thick, containing a moist, pink kernel. Farmer and Sunderland (*J.*, 1935, 759) found 44% of oil in the kernels. In a private communication Mr. G. Winter writes: "We had obtained a parcel of seeds from New Guinea, which contained seeds which had been collected in various areas of the territory. Examining individual seeds we found the oil content to vary from 3% to 40% of the kernel, the majority being between 20% and 35%. There was also great difference between individual seeds in the shell : kernel ratio. So far, we have not been able to distinguish between high and low oil-bearing seeds according to general appearance, size, or shape. According to Mr. Parham of the Department of Agriculture, Fiji, four varieties of *Parinarium laurinum* are known, all of which bear similar fruit, but differ in the shape of the leaves." The properties of the oil and its actual and possible uses have been discussed in two recent reviews (Anon., *Paint Manuf.*, 1945, **15**, 356; Winter, Nunn, and Ward, *Paint Notes, Austral.*, 1948, **3**, 393).

The chemical composition of the component acids of the oil was first examined by Tsujimoto and Koyanagi (*J. Soc. Chem. Ind. Japan*, 1933, **36**, 110, 673), who crystallised the mixed fatty acids from light petroleum and isolated an acid of melting point 85—86°, which they named parinaric acid but considered to be a geometrical isomer of elaeostearic acid. The same acid was also isolated by Farmer and Sunderland (*loc. cit.*) in 24% yield from the mixed fatty acids of the oil. These workers were able to show that, on hydrogenation, parinaric acid absorbed 4 molecules of hydrogen, yielding stearic acid. Oxidation by alkaline permanganate yielded azelaic, propionic, and oxalic acids, they therefore concluded that parinaric acid is octadeca-9 : 11 : 13 : 15-tetraenoic acid.* These findings were later supported by Kaufmann, Baltes, and Funke (*Fette u. Seifen*, 1938, **45**, 302), who showed that the ultra-violet absorption spectrum of parinaric acid was very similar to that of decatetraene and concluded that the acid contains four conjugated double bonds.

More recently the absorption spectrum of the mixed fatty acids from the oil has been examined by Winter (*Paint Notes, Austral.*, 1948, **3**, 393) who concluded that, besides parinaric acid (46%), there was also present about 34% of a conjugated trienoic acid—probably α-elaeostearic acid.

The present part of this work has as its aims the identification of the component fatty acids present in the oil, and their determination. Three samples of oil have been studied, two of which were extracted in Australia by Winter, and a third which was extracted in Liverpool from seeds collected near Suva. In Table I are given the physical constants of the oils, together with those reported by other workers.

TABLE I.

Sample.	I.	II.	III.	IV.	V.
% of oil in dry kernels	12·9	12	—	—	17·6
n^{40}	1·5510	1·5527	1·5480	1·5610 [b]	1·5610 [c]
Free fatty acid (as oleic), %	18·8	—	2·8	0·6	5·9
I val.	180·8 [a]	179·0 [a]	176·8 [a]	214·4	185 [d]
I val. (Toms)	240·3	255·8	229·3	—	—
Unsaponifiable matter, %	—	1·0	0·9	1·15	0·9

[a] 20 c.c. of Wijs reagent (200% excess) on 0·1 g. of fat; reaction period, 30 minutes.
[b] At 50°. [c] At 15°. [d] Wijs reagent (200% excess) for 1 hr. at 20°.

I. Seeds collected near Suva and extracted in Liverpool.
II. Oil extracted in Australia from seeds collected near Suva (Fiji).
III. Oil extracted in Australia from seeds collected in Fiji.
IV. Tsujimoto and Koyonagi (*loc. cit.*).
V. Winter's (*loc. cit.*) seed collected near Suva.

There thus seems to be reasonable agreement between the values recorded by the various workers, for all the constants, except the free acidity and iodine values. The free acidity depends greatly on the maturity of the seeds, and their method of collection and storage, and the iodine value varies, when unsaturated acids having conjugated double bonds are present, with the reagent used, its excess, and the time of reaction.

Pure parinaric acid, m. p. 86°, has been isolated by repeated crystallisation of the mixed fatty acids from light petroleum and ether. The acid has been subjected to acetone-permanganate oxidation, yielding azelaic acid as the sole dibasic acid, which confirms the structure for the acid proposed by Farmer and Sunderland (*loc. cit.*). The ultra-violet absorption spectrum of the

* In this paper numbering is according to the Geneva system, the number 1 being assigned to CO_2H.

acid (Fig. 1.) agreed fairly well with the observations of Kaufmann *et al.* (*loc. cit.*) and Winter (*loc. cit.*) (see Table II).

TABLE II.

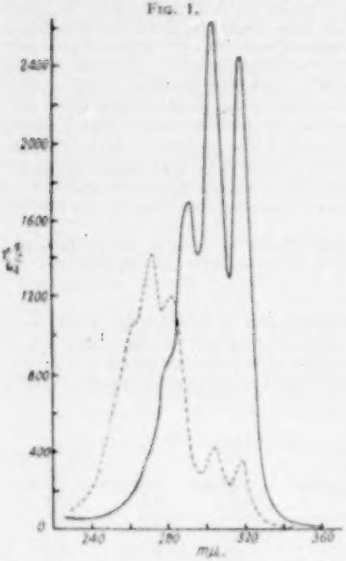
Absorption spectrum of parinaric acid.

	$\lambda_{max.}$ at mμ.	$E^{1\%}_{1\ cm.}$	$\lambda_{max.}$ at mμ.	$E^{1\%}_{1\ cm.}$	$\lambda_{max.}$ at mμ.	$E^{1\%}_{1\ cm.}$
Present work	291·5	1694	305	2624	320	2450
Kaufmann *et al.* (*loc. cit.*)	—	—	307	—	—	—
Kaufmann & Keller [1]	292·5	1906	306·5	2800	321·5	2400
Winter (*loc. cit.*)	293	1820	305	2800	319	2500

[1] *Ber.*, 1948, **81**, 152 (in heptane).

The isolation, in a pure state, of the triene acid present in the mixed fatty acids has not proved possible, either by crystallisation or by chromatographic adsorption on silica gel. The difficulty of separation is largely due to the extremely labile nature of the parinaric and triene acids, and partly to the comparatively small difference in solubility. Nevertheless a concentrate containing 76% of conjugated triene with 16% of parinaric acid has been obtained by crystallisation. This acid shows an absorption spectrum having maxima at the same wavelengths as α-elaeostearic acid (Fig. 1). The methyl ester of the concentrate on oxidation by means of permanganate in acetone yielded azelaic acid as the sole dibasic acid in amount considerably greater than would have been yielded by the parinaric acid present. The triene acid must therefore have its double bonds in the 9 : 11 : 13-positions, and thus be either α-elaeostearic acid or a *cis-trans*-isomer thereof. Its identity as α-elaeostearic acid has been proved by its conversion into its maleic anhydride adduct, which after crystallisation from light petroleum had melting point 62°, and did not depress the melting point (62—63°) of an authentic specimen. The absorption spectra of the two maleic anhydride adducts were identical (Fig. 2). Parinaric acid, when treated with maleic anhydride under the same conditions, yielded only a brownish resin, insoluble in light petroleum.

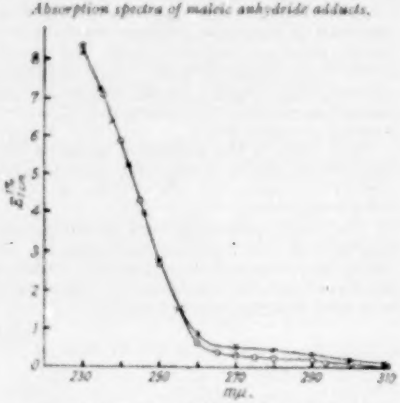
FIG. 1.



Absorption spectra of pure parinaric acid, continuous line. Concentrate of trienoic acid, broken line.

FIG. 2.

Absorption spectra of maleic anhydride adducts.



○ *Triene acid in* P. laurinum *oil.*
· *Authentic α-elaeostearic acid.*

A small amount of conjugated dienoic acid also occurs in the mixed acids, as shown by a maximum in the absorption curve at 234 mμ. It has not been possible to obtain a sufficiently high concentration of the acid for it to be identified, but by analogy it is probably octadeca-9 : 11-dienoic acid. The spectrum of the mixed acids has been examined without success for the presence of conjugated pentaenoic or more unsaturated acids.

The non-conjugated unsaturated acids present have been shown by conversion into di- and tetra-hydroxystearic acids (by oxidation of concentrates of the acids with dilute alkaline permanganate) to be the normal oleic and linoleic acids occurring in seed oils. On bromination of the concentrate in ether, no insoluble hexabromides were obtained, agreeing with the findings of Hilditch and Riley (*J. Soc. Chem. Ind.*, **1940**, **65**, 74T) that linolenic acid does not occur in the presence of α-elaeostearic acid.

The principal saturated acid present in the oil has been shown—after hydrogenation and fractionation of the methyl esters of the mixed acids—to be palmitic acid. Small amounts of lower saturated acids also occur in the oil; these have not been identified, but are probably oxidation products of the parinaric acid.

The compositions of the mixed acids from two of the samples of oil have been determined by a modification of the methods used by Hilditch and Riley (*loc. cit.*) for the examination of oils containing elaeostearic acid. The mixed acids were resolved into fractions by crystallisation from light petroleum and acetone at low temperatures, before spectroscopic examination. The parinaric acid was determined by the absorption of the alcoholic solution at 305 mμ. After allowance has been made for its absorption at 270 mμ. (band-head of α-elaeostearic acid) and at 234 mμ. (band-head of conjugated diene), the elaeostearic and conjugated dienoic acids were determined. Similar corrections were applied to the values obtained by alkali isomerisation for the determination of linoleic and linolenic acid. Values used in the calculations, determined with pure parinaric acid, are given in Table III (values used in the calculation of results are given in bold type).

TABLE III.

$E^{1\%}_{1\,cm.}$ for pure parinaric acid.

$E^{1\%}_{1\,cm.}$ at	234 mμ.	270 mμ.	291·5 mμ.	305 mμ.	320 mμ.
Untreated	**53·6**	**386**	1694	**2624**	2450
Alkali-treated, 170°/15 mins.	90·6	**452**	—	—	—
Alkali-treated, 180°/60 mins.	**91·0**	—	681	744	473

Saturated acids were determined in each case by the Bertram method (*Z. deutsch Oel Fett Ind.*, **1925**, **45**, 733) and palmitic acid by fractionation of the hydrogenated methyl esters as proposed by Gunstone and Hilditch (*J. Soc. Chem. Ind.*, **1946**, **65**, 8T).

From the data obtained the component fatty acids (excluding unsaponifiable matter) of the two oils have been deduced (see Table IV).

TABLE IV.

Component fatty acids of Parinarium laurinum *(excluding unsaponifiable matter).*

	Sample II (from Suva).	Sample III.
Palmitic + stearic	4	5
Oleic	6	10
Linoleic	2	2
Linolenic	—	—
Conjugated octadecadienoic	1	2
α-Elaeostearic	31	30
Parinaric	56	51

From these figures it will be seen that there is comparatively little difference between the two oils, although the proportion of parinaric acid is rather variable. The analysfs confirms the deduction made from bromination, that linolenic acid is absent. It is thus evident that *P. laurinum* is similar to many other members of the *Parinarium* species in containing α-elaeostearic acid, with lesser amounts of linoleic, oleic, and palmitic acid, but is so far as is known almost unique in also containing the conjugated tetraenoic parinaric acid. Parinaric acid has, however, been reported in the seed fats of *P. glaberrimum* and *P. scabium* (Frahm, *De Ingenieur in Nied-Indie*, **1941**, **7**, 42) and of a few members of the Balsaminaceæ, *e.g.*, *Impatiens Roylei Walpers* (Kaufmann and Keller, *loc. cit.*).

Since the completion of this work the following private communication has been received from Mr. Winter: "Some (*P. laurinum*) fats when examined spectrophotometrically were

found to contain more trienoic than tetraenoic acid, in others again there was hardly an inflexion at the 271·5-mμ. band and the spectrum showed only the characteristic maxima for the tetraene acid. The unfortunate part, however, is that there appears to be no correlation whatsoever in these differences with the appearance, size, or shape of the seeds."

Experimental.

The following data were obtained on the oil extracted by light petroleum (sample III) in Australia, and similar results were obtained for the oil sample from Suva (sample II).

Characteristics of the Oil.—Iodine value (Wijs, on a 0·1-g. sample for 30 minutes) 176·8, iodine value (Toms) 229·3, free fatty acid (as oleic) 2·8%, unsaponifiable matter (by Society of Public Analysts' method (*Analyst*, 1933, **58**, 209)) 0·9%, n^{40} 1·5480, total saturated acids (Hertram) 5·2%.

Hydrolysis of the Oil and Low-temperature Crystallisation of the Mixed Acids.—The oil (46·9 g.) was neutralised with potassium hydroxide solution, and the neutral oil hydrolysed by boiling it under reflux for an hour with a solution of 25 g. of potassium hydroxide in 250 ml. of alcohol. The acids were liberated from the soaps with sulphuric acid and extracted with ether as rapidly as possible to prevent polymerisation. After removal of the ether the acids were preserved in the dark in a well-corked flask filled with carbon dioxide and stored on solid carbon dioxide until required, to prevent the polymerisation of parinaric acid.

The mixed acids (42·53 g.) from the oil were boiled with 350 ml. of light petroleum, and the solution decanted from the resinous polymerised material P_1, the latter was washed twice with 40 ml. of boiling light petroleum, and the washings added to the main solution. The solution of the acids in light petroleum was crystallised at −25°, and the deposited acids (36·52 g.) were recrystallised from light petroleum (50 ml./g.) at 0°, yielding crystallised acids *A* (22·17 g.), polymerised material P_2 (0·90 g.) (which was combined with P_1; total, 2·62 g.), and soluble acids (13·45 g.). The soluble acids were recrystallised from light petroleum (20 ml./g.) at −35°, giving crystallised acids *B* (12·18 g.) and soluble acids *C* (1·27 g.). The soluble acids (4·29 g.) from the crystallisation from light petroleum (10 ml./g.) at −25° were recrystallised from acetone (10 ml./g.) at −60°, yielding insoluble acids *D* (1·19 g.) and soluble acids *E* (3·10 g.). Data for these fractions are given in Tables V, VI, and VII.

Table V.

Crystallisation data.

Fraction.	Wt., g.	%	I val. (Toms).
A	22·17	52·1	—
B	12·18	28·7	—
C	1·27	3·0	176·2
D	1·19	2·8	—
E	3·10	7·3	196·3
P_1	1·72	4·0	—
P_2	0·90	2·1	—
	42·53		

Table VI.

Spectrographic examination of fractions.

	Untreated.				Alkali isomerised at 170° for 15 mins.	Alkali isomerised at 180° for 60 mins.
Fraction. $E^{1\%}_{1cm.}$ at	234	270	305	320	270	234 mμ.
Mixed acids *	100·5	667	1267	1106	687	120·8
A	97·0	539	1945	1725	569	106·8
B	142·2	1029	612	509	952	151·9
C	155·9	749	283	206	699	223
D	96·4	890	123·0	95·3	835	128·9
E	127·0	632	324	245	615	265

* Including polymerised.

Table VII.

Component acids of fractions (% wt.).

	Mixed acids.*	*A.*	*B.*	*C.*	*D.*	*E.*
Saturated Oleic Unsaponifiable	22·5	9·4	21·3	36·1	43·2	35·1
Linoleic	0·7	—	0·9	7·8	5·1	15·3
Linolenic	—	—	—	—	—	—
Conjugated dienoic	1·5	2·3	1·7	5·6	—	4·3
Conjugated trienoic	27·0	14·2	52·8	39·7	49·0	33·0
Parinaric	48·3	74·1	23·3	10·8	4·7	12·3

* Including polymerised.

Determination of Palmitic Acid by Hydrogenation.—The refined oil (53 g.) was hydrogenated at 100° with Raney nickel, and the product [I val. (Wijs), 100·3] was saponified. The acids were converted into the methyl esters, which were rehydrogenated at 100°. The product (I val., 12·1) was fractionated as proposed by Gunstone and Hilditch (*loc. cit.*); 4·2% of palmitic acid were present, together with a quantity of polymerised matter (see Table VIII).

TABLE VIII.

Fractionation of hydrogenated methyl esters of Parinarium laurinum *oil.*

No.	G.	Sap. equiv.	I val.	Palmitic.	C_{18}.
*H*1	1·97	276·1	4·6	1·50	0·47
*H*2	2·80	295·5	1·7	0·23	2·57
*H*3—*H*12	31·85	299·1—326·6	1·8—12·9	—	31·85
Residue	4·97	376·2	66·5	—	4·97
Total	41·59		Total	1·73	39·86
			Palmitic acid, %	4·2	95·8

From the above results, the composition of the mixed acids of the oil was calculated to be as shown in Table IX.

TABLE IX.

Component acids of Parinarium laurinum *seed fat* (%, wt.).

Fraction:	*A*. (52·1%).	*B*. (28·7%).	*C*. (3·0%).	*D*. (2·8%).	*E*. (7·3%).	P_1+P_2 (0·1%).	Total.	Acids including unsaponifiable, % (wt.).
Palmitic	4·90	6·11	1·08	1·21	2·55	—	4·20	4·2
Stearic							1·00	1·0
Unsaponifiable							0·90	—
Oleic							9·75	9·9
Linoleic	—	0·26	0·23	0·09	1·13	—	1·71	1·7
Conj. dienoic	1·20	0·49	0·17	—	0·31	—	2·17	2·2
Conj. trienoic	7·40	15·15	1·19	1·37	2·41	—	27·52	30·1
Parinaric	38·60	6·69	0·33	0·13	0·90	—	46·65	50·9
Polymerised *	—	—	—	—	—	6·10	6·10 *	—

* The polymerised acids have been assumed to arise from elaeostearic and parinaric acids in the relative proportions observed for these acids.

Identification of Acids.—Palmitic acid. Fraction *H*1 (1·31 g.; Table VIII) was redistilled through a micro-distillation apparatus, yielding a fraction (0·37 g.) of sap. equiv. 272·9, which was converted into its *p*-bromophenacyl derivative; after recrystallisation from alcohol this had m. p. 82—83·5° alone or mixed with *p*-bromophenacyl palmitate (m. p. 83·5—84°).

Parinaric acid. (i) Crystallisation fraction *A* (Table V) was recrystallised repeatedly from light petroleum and ether, and yielded parinaric acid, m. p. 86°, $E^{1\%}_{1\,cm.}$ 2624 at 305 mμ.; these values could not be increased by further crystallisation. The above spectrographic value was the mean obtained by triplicate determinations (ranging from 2604 to 2644) on four preparations of parinaric acid.

(ii) *Oxidation of methyl parinarate.* Parinaric acid (7·00 g.) was esterified with methyl alcohol containing 0·5% of hydrogen chloride. The resultant esters (4·91 g.) were oxidised in solution in 100 ml. of acetone with 50 g. of potassium permanganate. There was obtained 1·00 g. of crude dibasic acid, together with a considerable amount of ether-insoluble polymerised material. The acid on recrystallisation from 100 ml. of water yielded 0·31 g. of azelaic acid, m. p. 102—104° alone or mixed with authentic material (m. p. 103—105°). Parinaric acid (17·95 g.) on oxidation under the same conditions yielded 4·63 g. of crude azelaic acid, which on recrystallisation from water had m. p. 103—104°.

(iii) *Combination of parinaric acid with maleic anhydride.* Parinaric acid (2·80 g., 0·01 mol.) was heated to 100° for 5 minutes in an atmosphere of carbon dioxide with maleic anhydride (2·1 g., 0·0215 mol.). The resultant dark viscous fluid, which was insoluble in light petroleum, solidified in 2 days to a hard brittle resin.

α-Elaeostearic acid. (i) *Preparation of a concentrate of the trienoic acid.* The mixed acids (133 g.) from the oil were crystallised from 2660 ml. of light petroleum at 0°. The resultant filtrate was then cooled to −15°, and a further crop of crystals (12·8 g.) removed. The volume of the filtrate was reduced to 800 ml., and the solution cooled to −65°. The deposited crystals (34 g.) were recrystallised from light petroleum (900 ml.) at −45° and then from 300 ml. of ether at −20°. The soluble acids (23·2 g.) from the ether crystallisation were twice crystallised from acetone at −15° and then at −75°. The crystalline product (14·5 g.) had $E^{1\%}_{1\,cm.}$ 1409 at 270·5 mμ. and 428 at 305 mμ., corresponding with 76·3% of α-elaeostearic and 16·3% of parinaric acid. This concentrate was used for the characterisation of the triene acid.

(ii) *Oxidation of the concentrate.* The methyl ester (5·14 g.) of the concentrate was oxidised in 50 ml. of acetone with 35 g. of potassium permanganate. The crude dibasic acid (1·50 g.) after recrystallisation from 100 ml. of water yielded 0·555 g. of azelaic acid, m. p. 103—105° (mixed m. p. undepressed).

(iii) *Preparation of the maleic anhydride adduct of the trienoic acid.* The concentrate (3·28 g.) was heated with maleic anhydride (0·72 g.) at 105° for 15 minutes in a current of carbon dioxide. The cooled mixture was boiled twice with light petroleum (100 ml.), and the clear liquid decanted from the

small amount of insoluble oil. On cooling, there separated from the light petroleum 0·5 g. of a white crystalline adduct, which was twice recrystallised from 140 ml. of light petroleum, yielding 0·38 g. of adduct, m. p. 62—63° (undepressed by the maleic anhydride adduct of α-elaeostearic acid, m. p. 62—63°).

(iv) *Preparation of maleic anhydride addition compound of α-elaeostearic acid.* α-Elaeostearic acid (2·76 g., 0·01 mol.), $E^{1\%}_{1cm}$ 1795 at 270·5 mμ, was heated with maleic anhydride (1·0 g., 0·0102 mol.) at 105° for 15 minutes. The adduct was separated and recrystallised as above, yielding 0·31 g. of colourless adduct, m. p. 62—63° (Morrell and Samuels, *J.*, 1932, 2251, record m. p. 62·5°). The ultra-violet absorption spectra of this compound and the adduct from the concentrates of the triene acid were identical.

Linoleic and oleic acid. Preparation of a concentrate of linoleic and oleic acid. The mixed acids (210 g.) from the oil were crystallised from 2·5 l. of light petroleum at −70°, and the resultant liquid acids (90·5 g.) were recrystallised from 400 ml. of light petroleum at −60°. The filtrate from this crystallisation (11·9 g., I val. (Toms), 135·9), which contained linoleic 17·3, parinaric 3·2, α-elaeostearic 15·2, and conjugated dienoic acids 5·5%, was employed for the characterisation of oleic and linoleic acid.

(i) *Bromination (detection of linoleic acid).* The concentrate (3·05 g.) was brominated in 60 ml. of light petroleum at −10° with 0·82 ml. of bromine. The clear liquid was decanted from the deposited oil and set aside overnight at 0°. 0·29 G. of crystalline bromides separated. The latter were recrystallised from 10 ml. of ether at −40°, yielding 0·102 g. of 9 : 10 : 12 : 13-tetrabromostearic acid, m. p. 113·5—114° alone or mixed with authentic tetrabromostearic acid, m. p. 114°. Complete solubility of the bromides in ether indicated the absence of hexabromostearic acid, and hence of linolenic acid from the oil.

(ii) *Oxidation with dilute alkaline permanganate.* The concentrate (7·37 g.) was oxidised by the method of Lapworth and Mottram (*J.*, 1925, **127**, 1628). There were recovered 1·63 g. of hydroxy-acids and 2·13 g. of saturated and unoxidised acids. On recrystallisation of the former from water and ethyl acetate, 0·80 g. of dihydroxystearic acid, m. p. 132°, was obtained (mixed m. p. with 9 : 10-dihydroxystearic acid, m. p. 132°, undepressed). In addition the two 9 : 10 : 12 : 13-tetrahydroxystearic acids, m. p. 153° (0·32 g.) and 173° (0·13 g.), formed by the oxidation of linoleic acid, were also recovered.

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5. *Hydrolyses and Derivatives of Some Vesicant Arsenicals.*

By William A. Waters and J. Howarth Williams.

The hydrolyses of pure 2-chlorovinyldichloroarsine (Lewisite-I) and of phenyldichloroarsine have been studied by using the partitions of their solutions between benzene and water. Several dialkyloxy-derivatives of Lewisite-I, and some analogous dithiols, have been made, and it has been found that dithiocarbamates are particularly useful for characterising the arsenical vesicants.

Lewisite-I gives a characteristic solid with dioxan, and arsenic trichloride with thioxan.

Hydrolysis of β-Chlorovinyldichloroarsine.—The hydrolysis of Lewisite-I by water involves the following equilibria :

$$\mathrm{ClCH{:}CH{\cdot}AsCl_2} + 2\mathrm{H_2O} \overset{\text{(fast)}}{\rightleftharpoons} \mathrm{Cl{\cdot}CH{:}CH{\cdot}As(OH)_2} + 2\mathrm{HCl}$$

$$\underset{\text{(I.)}}{\mathrm{Cl{\cdot}CH{:}CH{\cdot}As(OH)_2}} \overset{\text{(slow)}}{\rightleftharpoons} \mathrm{H_2O} + \underset{\text{(II.)}}{\mathrm{Cl{\cdot}CH{:}CH{\cdot}AsO}} \overset{\text{(slow)}}{\rightleftharpoons} \underset{\text{(III.)}}{(\mathrm{Cl{\cdot}CH{:}CH{\cdot}AsO})_n}$$

The only substance which can be isolated is polymerised 2-chlorovinylarsinoxide (III), a white insoluble powder of indefinite m. p. Measurements of the equilibria, however, indicate that both the hydroxide (I) and the unpolymerised oxide (II) must be capable of existence in solution in water and benzene respectively.

On treatment with water, Lewisite-I immediately gives a strongly acid solution and a sticky gum, consisting of unchanged Lewisite and (III). If however Lewisite-I is mixed with benzene and then treated with water two clear liquid layers are obtained which, when shaken, rapidly attain an equilibrium which is independent of the initial concentration of the Lewisite-I in the benzene layer. Both the layers can be analysed for (i) chlorine content, (ii) acidity, and (iii) tervalent arsenic by titration with silver nitrate, alkali, and iodine, respectively, and in this way the equilibria attained in the hydrolysis can be found. Figs. 1 and 2 show the results obtained.

The equilibrium attained on shaking a benzene solution of Lewisite-I with aqueous hydrochloric acid corresponds exactly to that reached on shaking a corresponding amount of Lewisite-I with a proportionately smaller volume of water; that is, the percentage of Lewisite-I which

remains as such in the benzene layer depends only on the acidity, the bulk of the aqueous layer being immaterial.

FIG. 1. FIG. 2.

Hydrolysis of Lewisite-1 in benzene at 17° in ½ hour.

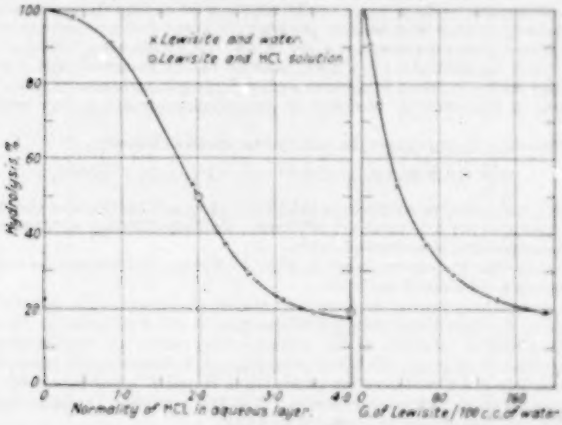
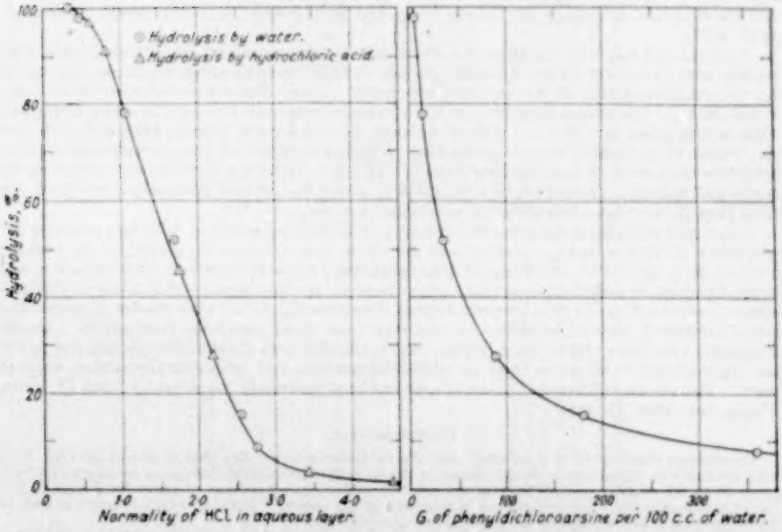


FIG. 3. FIG. 4.

Hydrolysis of phenyldichloroarsine in benzene at 15°.


○Hydrolysis by water.
△Hydrolysis by hydrochloric acid.
Hydrolysis, %
Normality of HCl in aqueous layer.
G. of phenyldichloroarsine per 100 c.c. of water.

The hydrolysis of phenyldichloroarsine has been studied in a similar way, giving results which are shown in Figs. 3 and 4.

The evidence for the separate existence of the dihydroxide (I) is as follows. A 4% solution

of Lewisite-I oxide (possibly II) in benzene can be obtained by boiling the dry polymerised oxide (III) for a long time with this solvent. The solution is vesicant, and on storage deposits colourless crystals which soon change to the amorphous white polymer. When this benzene solution is shaken with water the arsenic content of the benzene drops *slowly* during some hours. Only a 1% solution of lewisite oxide in water can be obtained by leaving the constituents in contact. When this solution is shaken with benzene the arsenic content of the benzene slowly rises during some hours. The aqueous solution has a pH of 6·8, but by allowing Lewisite-I to remain in contact with water containing chalk a 2·8% solution can be obtained; and a solution of still higher normality can be obtained in aqueous sodium hydrogen carbonate of pH about 8. Thus the dihydroxide of Lewisite-I is, like that of phenyldichloroarsine, a very weak acid giving soluble salts.

Lewisite-I *however* is decomposed by *cold* caustic alkali as follows:

$$Cl{\cdot}CH{:}CH{\cdot}As(OH)_2 + (OH)^- \longrightarrow Cl^- + C_2H_2 + As(OH)_3$$

In the cold (16°), only alkaline solutions of pH 10·5 or more will bring about this decomposition, but at 50° solutions of pH 9 or more are effective. Prolonged boiling with water alone brings about some decomposition of Lewisite-I oxide.

It is significant that the curves shown in Figs. 1—4 show no irregularities indicative of the existence of hydroxy-chlorides R·AsCl·OH.

Alkyl-oxy- and -thio-derivatives of Lewisite-I and its Analogues.—The vesicant character of arsenicals such as Lewisite-I and phenyldichloroarsine is not a property of the $AsCl_2$ group, since carefully prepared solutions of the corresponding oxides or dihydroxides are equally vesicant. In order to enhance the lipoid solubility of 2-chlorovinyldihydroxyarsine and its analogues, a number of derivatives of the general type $R{\cdot}As(OR')_2$ has been made by the action of sodium alkoxides on the arsenical vesicants. The products are all volatile, vesicant, liquids which are hydrolysed *irreversibly* on contact with water.

A number of analogous thioethers $R{\cdot}As(SR')_2$ has also been made. These are very slightly soluble in water and in general are hydrolysed *reversibly*, giving toxic, and sometimes vesicant, solutions, though the equilibrium $R{\cdot}As(SR')_2 + 2H_2O \rightleftharpoons R{\cdot}As(OH)_2 + 2R'SH$ generally favours thioether formation (cf. Cohen, King, and Strangeways, *J.*, **1931**, 3043; Barber, *J.*, **1932**, 1365).

Aqueous and alcoholic solutions of sodium diethyldithiocarbamate, and its analogues, react readily with Lewisite-I to give crystalline solids of sharp melting-point which are very useful for the characterisation of the arsenical war gases. These dithiocarbamates are much more stable than are the simple thioethers of the alkyldichloroarsines, but only in cyclic structures, such as that given by "B.A.L." (Peters, Stocken, and Thompson, *Nature*, 1945, **136**, 616) does the degree of hydrolysis become negligible. Alkali hydrolyses all these compounds rapidly, acetylene being evolved from the Lewisite-I derivatives. Hydrogen peroxide also breaks up the ethers and thioethers in neutral or acid solution, giving free arsonic acids which are much less toxic than the corresponding tervalent substituted arsines.

Compound Formation with Dioxan.—When pure Lewisite-I is mixed with an equimolecular proportion of dioxan, heat is evolved and the whole mass solidifies on cooling to an addition product, m. p. 58—59°. This however dissociates into its constituents both when vaporised and when dissolved in anhydrous solvents such as benzene or chloroform. Di-2-chlorovinylchloroarsine (Lewisite-II) and tri-2-chlorovinylarsine (Lewisite-III) do not give similar products, and hence Lewisite-I may be separated in this way from these associated compounds. Arsenic trichloride also forms crystalline addition compounds with both dioxan and thioxan, but few of the other arsenical war gases, such as ethyldichloroarsine and phenyldichloroarsine, seem to react. The arsenic trichloride–dioxan adduct has been previously described by Doak (*J. Amer. Pharm. Soc.*, **1934**, **23**, 541).

Experimental.

Quantitative Hydrolysis of Lewisite-I and Phenyldichloroarsine.—The results shown in Figs. 1—4 were obtained by dissolving a weighed amount of carefully fractionated Lewisite-I or phenyldichloroarsine in 50 ml. of benzene and shaking the solution with a known volume of water for ½ hour at 17°. Figs. 1 and 3 show the relation between the amount of the vesicant, $R{\cdot}AsCl_2$, which remains as such in the benzene layer and the acidity attained by the aqueous layer.

The points indicated as "hydrolysis by hydrochloric acid" show that the degree of hydrolysis depends on the acidity of the aqueous phase and not on its total volume. Figs. 2 and 4, which refer to hydrolysis by water alone, show the extent to which the vesicants are hydrolysed on admixture with limited quantities of water. Again the degree of hydrolysis is independent of the initial concentration in the benzene layer.

Arsine, AsR_3.	B. p.	Formula.	Found. C, %	H, %	As, %	Cl, %	Equiv.	Required. C, %	H, %	As, %	Cl, %	Equiv.
Dimethoxy-2-chlorovinyl-	59°/6 mm.	$C_4H_8O_2ClAs$	—	—	—	17·8	98·6	—	—	—	17·9	99·2
Diethoxy-2-chlorovinyl-	71°/3 mm.	$C_6H_{12}O_2ClAs$	—	—	—	15·5	113	—	—	—	15·7	113
Diisopropoxy-2-chlorovinyl-	80°/3 mm., 88°/6 mm.	$C_8H_{16}O_2ClAs$	—	—	—	13·8	127	—	—	—	13·9	127
Diamyl-2-chlorovinyl-	130—138°/3 mm.	$C_{12}H_{24}O_2ClAs$	—	—	—	—	155	—	—	—	—	155
Diisooctyl-2-chlorovinyl-	184—186°/2 mm.	$C_{16}H_{32}O_2ClAs$	—	—	—	—	198	—	—	—	—	197
Diallyl-2-chlorovinyl-	99°/4 mm.	$C_8H_{12}O_2ClAs$	—	—	—	13·9	125	—	—	—	14·2	125
Di-(2-ethoxyethoxy)-2-chlorovinyl-	150°/3 mm.	$C_{10}H_{20}O_4ClAs$	—	—	—	11·4	155	—	—	—	11·3	157
Dimethoxyethyl-	129°/760 mm.	—	—	—	44·1	—	—	—	—	44·4	—	—
Methoxydiphenyl-	138°/2 mm., 150°/7 mm.	$C_{19}H_{19}OAs$	—	—	—	—	130	—	—	—	—	130
Methyldimethoxy-	111°/760 mm.	$C_3H_9O_2As$	—	—	—	—	76	—	—	—	—	76
Methyldiethoxy-	137°/760 mm.	$C_5H_{13}O_2As$	—	—	—	—	89	—	—	—	—	90
Methyldimethylthio-	75—77°/2 mm.	$C_3H_9S_2As$	—	—	40·4	—	—	—	—	40·7	—	—
Methyldiphenylthio-	195—198°/1 mm.	$C_{13}H_{13}S_2As$	—	—	24·5	—	—	—	—	24·5	—	—
Methyldi-p-tolylthio-	230°/0·5 mm.	$C_{15}H_{17}S_2As$		(S, 18·4)					(S, 19·0)			
Diphenylthio-2-chlorovinyl-	180—190°/2 mm. (decomp.)	—										
Di-(NN-diethylthiocarbamylthio)-2-chlorovinyl- [1]	m. p. 87°	$C_{12}H_{22}ClS_2N_2As$	32·6	5·1	17·4	—	—	33·3	5·1	17·3	—	—
Di(morpholine-4-thiocarboxythio)methyl- [2]	m. p. 178°	$C_{11}H_{19}O_2S_6N_2As$	32·0	4·65	18·0	—	—	31·9	4·6	18·1	—	—
Di(morpholine-4-thiocarboxythio)ethyl- [3]	m. p. 154°	$C_{12}H_{21}O_2S_6N_2As$	33·5	5·0	17·3	—	—	33·6	4·9	17·5	—	—
Di(morpholine-4-thiocarboxythio)-2-chlorovinyl- [4]	m. p. 161°	$C_{12}H_{18}O_2ClS_6N_2As$	31·3	4·0	16·2	—	—	31·3	3·9	16·3	—	—
Di(morpholine-4-thiocarboxythio)phenyl- [5]	m. p. 218—219°	$C_{14}H_{21}O_2S_6N_2As$	40·5	4·45	15·9	—	—	40·3	4·4	15·8	—	—

[1] $[O<[CH_2]_2>N\cdot CS\cdot S]AsR$. [2] $(NEt_2\cdot CS\cdot S)_2As\cdot CH{:}CHCl$, crystd. from EtOH (Found: S, 29·4. Reqd.: S, 29·6%). [3] Needles from aqueous acetone. [4] Prisms from aqueous acetone. [5] Highly refracting rectangular plates. [6] Small needles or spherical aggregates.

Partition Coefficient of Lewisite-I Oxide.—The solution of the oxide in water was shaken with benzene, and samples of each layer, removed at intervals, were analysed for arsenic by addition of excess of iodine and back-titration with standard arsenite solution in the presence of sodium hydrogen carbonate. The following figures show that the equilibrium between the benzene-soluble oxide and the water-soluble dihydroxide is attained only slowly.

	Partition coefficient, $C_{H_2O}/C_{C_6H_6}$.			
Time of shaking (mins.)	10	60	120	1020
Initial aqueous solution + Benzene	8·13	4·74	2·63	1·67
Initial benzene solution + Water	0·07	0·23	0·26	0·69

The influence of the hydrogen carbonate buffer on the partition coefficient is shown by the following figures:

Lewisite + benzene + excess of aqueous $NaHCO_3$: $C_{H_2O}/C_{C_6H_6}$ 13·5
Lewisite oxide (II or III) in benzene + aqueous $NaHCO_3$: $C_{H_2O}/C_{C_6H_6}$ 13·4

Fission of Lewisite-I by the Hydroxyl Ion.—Lewisite-I hydroxide solution was prepared by adding 1 g. of Lewisite-I to 400 ml. of very dilute sodium hydrogen carbonate solution, shaking the mixture until reaction was complete, and acidifying cautiously with dilute hydrochloric acid until pH 7 was reached (B.D.H. Universal Indicator). 10-Ml. samples of this solution were added to 20 ml. of a buffer and maintained at 17°. Fission was detected by adding to each solution 1 ml. of ammoniacal cuprous chloride solution. A reddish-brown precipitate of cuprous acetylide indicated that fission had occurred. Results were:

Buffer used.	Reaction time (hours) before test.			
	2	6	17	24
4% Na_2HPO_4, pH 8·5	—	—	—	—
4% Borax, pH 9·5	—	—	Trace	Slight
4% K_2CO_3, pH 10·5	+	+	+	+

From similar experiments at 50° it was found that at this temperature fission was appreciable at pH 9·5 after 1 hour; 1% (or stronger) solutions of sodium carbonate gave evidence of fission at 50° after only 15 minutes.

A 4% solution can be obtained by boiling Lewisite-I oxide (III) with water for some time; if, however, the evolved vapours are led into ammoniacal cuprous chloride solution a positive acetylene reaction is obtained though a solution of Lewisite-I oxide prepared in the cold gives no positive reaction with this reagent.

Lewisite-I itself, when similarly boiled with water, gives no positive reaction for acetylene.

When administered (*a*) as droplets of Lewisite to the skin, (*b*) by injection, or (*c*) as dihydroxide by mouth, to experimental animals, Lewisite-I is slowly excreted in the form of its water-soluble dihydroxide and can be detected throughout the digestive system and particularly in the urine, by the cuprous chloride reaction which is sensitive to 0·001 mg. and can be used for approximate quantitative assay.

Derivatives of Lewisite-I and its Analogues.—The new compounds shown in the table were prepared in the course of this investigation. Values recorded as As.% were determined iodometrically after destruction of organic matter. The values recorded as equiv. were obtained by titrating the compound directly with iodine, to covert ter- into quinque-valent arsenic.

Adducts with Dioxan and Thioxan.—When equimolar amounts of Lewisite-I and dry dioxan were mixed, considerable heat was generated and, on cooling, the mixture solidified to a mass of white crystals. Recrystallised from light petroleum (b. p. 40—60°) the *compound* formed long colourless needles, m. p. 58—59° (Found: C, 24·3; H, 3·5%; equiv. (As), 146, 148; equiv. (Cl), 148·5. $C_4H_{10}O_2Cl_2As$ requires C, 24·37; H, 3·80%; equiv. (Cl or As), 147·5). The "equiv. (As)" was determined as recorded above. The "equiv. (Cl)" was determined by titration in acid solution with silver nitrate, which reacts only with the chlorine bound to arsenic. The complex is almost completely dissociated in solution, as shown by molecular-weight determinations: Found: (cryoscopic in benzene) 145; (ebullioscopic in benzene) 195, 198; (ebullioscopic in chloroform) 124. Required: 124.

The arsenic trichloride dioxan complex, prepared in the same way, formed colourless crystals, m. p. 68—70°, from light petroleum, and had the composition assigned to it by Doak (*loc. cit.*) [Found: C, 23·0; H, 3·8%; equiv. (As), 158; equiv. (Cl), 105·0. Calc. for $3(C_4H_8O_2).2AsCl_3$: C, 22·9; H, 3·8%; equiv. (As), 156·6; equiv. (Cl), 104·4]. The molecular weight (cryoscopic in benzene) was 119; the required value is 627, so that the substance is strongly dissociated in solution, as stated by Doak.

The *arsenic trichloride–thioxan* complex, similarly prepared, formed colourless needles, m. p. 70—72° [Found: C, 16·8; H, 2·78%; equiv. (As), 143·5; equiv. (Cl), 96·0. $C_4H_8OSCl_3As$ requires C, 16·8; H, 2·8%; equiv. (As), 142·6; equiv. (Cl), 95·1]. Molecular-weight determination (cryoscopic in benzene) gave a value of 147 (Required: 285), again indicating almost complete dissociation.

The authors express their thanks to Mr. W. E. Hanby for assistance in the study of the hydrolysis of phenyldichloroarsine and to Mr. T. V. Healy for help in the preparation of a few of the dithiols. They thank the Chief Scientific Officer of the Ministry of Supply for permission to publish this paper, which describes work which was completed in 1939—40.

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6. *The Chemistry of Ribose and its Derivatives. Part II. The Constitution of an Anhydro-D-ribose.*

By G. R. Barker and M. V. Lock.

An anhydroribose prepared by the method of Bredereck, Köthnig, and Berger (*Ber.*, 1940, **73**, 956) has been examined and found to be bimolecular. Oxidation of the anhydride with sodium metaperiodate has been investigated and a crystalline *tetramethyl di-D-ribose anhydride* has been prepared and hydrolysed to 2 : 3-dimethyl D-ribose. Of three possible structures for the anhydride that corresponding to 1 : 5′-5 : 1′-diribofuranose anhydride is the most probable.

In an attempt to prepare 1 : 2 : 3-triacetyl D-ribofuranose by removal of the triphenylmethyl (trityl) grouping from 1 : 2 : 3-triacetyl 5-trityl D-ribofuranose, Bredereck, Köthnig, and Berger (*Ber.*, 1940, **73**, 956) obtained a compound which they claimed was 1 : 5-anhydro-D-ribofuranose. This structure was based on the failure of the compound to reduce Fehling's solution until after hydrolysis and a positive test for adjacent *cis*-hydroxyl groups with copper sulphate and alkali. However, it must be borne in mind that a number of different types of non-reducing anhydro-sugars are known, some monomeric and some dimeric, and that the structure postulated for the anhydroribose is by no means a unique interpretation of the experimental evidence. Our doubts as to the truth of the constitution assigned were aroused by the melting point of the compound (229—230°), which is unexpectedly high for a monomeric anhydride, compared with the melting point of D-ribose itself, variously given as 86—87° (Levene and Jacobs, *Ber.*, 1909, **42**, 1198) and 95° (van Ekenstein and Blanksma, *Chem. Weekblad*, 1913, **10**, 664). It was therefore decided to examine further the properties of the anhydride.

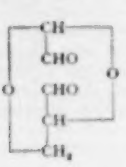
These studies have now reached a point at which it is clear that we have an anhydride not conforming in structure to that postulated by Bredereck and his co-workers. It will be seen from the results presented below that although it is probable we are dealing with the same compound we are unable to reproduce the specific rotation recorded previously. It is therefore considered desirable to place our observations on record in order that the question of the identity of the two materials may be considered by the German workers.

Trityl ribose and triacetyl trityl ribose were prepared and were found to correspond in properties with those previously recorded. By carrying out the acetylation without prior isolation of the trityl ribose the yield of the acetylated material was considerably improved. From triacetyl 5-trityl ribose prepared in either way were obtained an acetyl anhydroribose and an anhydroribose of which the melting points coincided with those recorded by Bredereck and his co-workers. The anhydroribose, however, had, in water, $[\alpha]_D^{20}$ +11°, whereas this was previously recorded as +78°. All other properties of our materials were identical with those recorded by Bredereck.

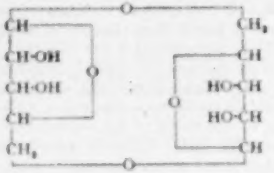
Oxidation of the anhydride by sodium metaperiodate resulted in the consumption of 1 mol. of oxidant per mol. of ribose and no formic acid was liberated. If the constitution put forward by Bredereck and his co-workers for the anhydroribose is correct, then the product of the above oxidation would be 2 : 4-diformyldioxolan (I), produced in a similar manner from *lævo*glucosan, D-altrosan, or D-mannosan. This compound is known to have $[\alpha]_D^{20}$ −15° (Jackson and Hudson, *J. Amer. Chem. Soc.*, 1940, **62**, 958; Richtmyer and Hudson, *ibid.*, p. 961; Knauf, Hann, and Hudson, *ibid.*, 1941, **63**, 1447), whereas the solution obtained after oxidising our anhydroribose with sodium metaperiodate had an observed rotation which corresponded to $[\alpha]_D^{15}$ −48°, calculated on the assumption of the presence of the above dialdehyde. It appeared improbable, therefore, that our anhydride had the structure claimed by Bredereck for his material. Furthermore, cryoscopic determination of the molecular weight of the anhydroribose in aqueous solution indicated that the compound was dimeric. The possibility that the compound was exhibiting an anomalous depression of freezing point in aqueous solution was excluded by the fact that cryoscopic determination of the molecular weight of the acetylated anhydride in benzene confirmed the dimeric nature of the material (cf. Jackson *et al.*, *J. Res. Nat. Bur. Stand.*, 1929, **3**, 27; 1930, **5**, 723; 1931, **6**, 709). It is concluded that the anhydroribose consists of two molecules of ribose united with loss of two molecules of water in such a way that both reducing groups are involved in the union and two pairs of adjacent hydroxyl groups are present in the molecule.

Hydrolysis of the acetylated anhydride with boiling aqueous acid, followed by examination of the hydrolysate on the paper chromatogram using Partridge's method (*Nature*, 1946, **158**, 270), indicated that ribose was the only fission product. The rotation of the solution was also in agreement with this conclusion. It appears therefore, that no ether bridge is present, but

that the ribose residues are joined by two glycosidic linkages. In order to establish which hydroxyl groups of the ribose radicals are thus combined in the anhydride, the tetra-acetyl diribose anhydride was methylated with methyl sulphate following Haworth and Streight's method (*Helv. Chim. Acta*, **1932**, **15**, 609, 693) and *tetramethyl di-D-ribose anhydride* was obtained which did not reduce Fehling's solution. This material was hydrolysed by boiling aqueous acid and the product, when examined on the paper chromatogram, moved as one component. In view of the observation of Hirst, Hough, and Jones (*J.*, **1949**, 928) that certain isomeric methylated sugars can be separated by partition chromatography, it seemed likely from the above results that tetramethyl di-D-ribose anhydride is split by acid hydrolysis into two identical molecules. Evidence in agreement with this view was obtained by further studies of the methylated anhydride. No dimethyl ribose has yet been described and, since it seemed highly



(I.)



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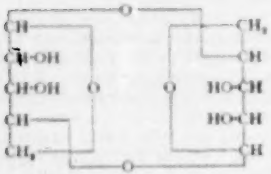
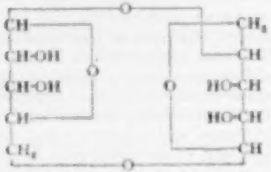


(III.)



(IV.)

probable that hydrolysis of the methylated anhydride would produce a dimethylated ribose, recourse was made to methods involving oxidation with the periodate ion. Moreover, a method was required whereby the homogeneity of the product of acid hydrolysis, suggested by partition chromatography, could be confirmed. Oxidation of the acid hydrolysate with periodic acid produced no formic acid, but 0·45 mol. of formaldehyde was produced as shown by the method of Jeanloz (*Helv. Chim. Acta*, **1944**, **27**, 1509). Both results indicate that two molecules of 2 : 3-dimethyl ribose are produced from the methylated anhydride by acid hydrolysis. First, during the oxidation of methylated sugars with the periodate ion, formic acid is produced by oxidation of a reducing group adjacent to a free hydroxyl group or of a 1 : 2 : 3-trihydric alcohol system. It can be concluded, therefore, that in the acid hydrolysate from the tetramethyl di-D-ribose anhydride there can be no ribose derivative in which position 2 is unmethylated, no monomethyl ribose, and no free ribose, any of which would have yielded formic acid. Since there are the four original methoxyl groups of the methylated anhydride to be accounted for, and no ribose or monomethyl ribose is present, the methylated anhydride must be split into two molecules of dimethyl ribose, both of which are methylated at position 2. Furthermore, since the anhydroribose itself consumes two mols. of sodium metaperiodate it must contain two 1 : 2-glycol groupings and hence the tetramethyl derivative possesses two pairs of adjacent methoxyl groups. 2 : 3-Dimethyl D-ribose, therefore, is the sole product of hydrolysis of tetramethyl D-diribose anhydride. The production of formaldehyde during the oxidation by periodic acid is also in agreement with this conclusion. Formaldehyde is produced by periodate oxidation of a 1 : 2-glycol of which one hydroxyl group is primary and, of those sugars allowed by the other evidence discussed above, this condition is fulfilled only by 2 : 3-dimethyl ribose. If, however, 2 : 3-dimethyl ribose is the sole product of acid hydrolysis of tetramethyl di-D-ribose anhydride, the production of two mols. of formaldehyde would be expected during the oxidation of the hydrolysate of this compound with periodic acid. The low yield of formaldehyde obtained in these experiments is consistent with previous findings (Bell, *J.*, **1948**, 992; Jeanloz, *loc. cit.*) that some methylated sugars are incompletely oxidised by periodic acid and it has been stated

(Bell, *loc. cit.*) that, while the detection of formaldehyde is a useful qualitative test for the presence of a free primary hydroxyl group, it is not susceptible of quantitative use. The low yield of formaldehyde is not, therefore, considered to alter in any way the validity of the previous statement that 2 : 3-dimethylribose is the sole product of hydrolysis from tetramethyl di-D-ribose anhydride.

From the results of the experiments summarised above it follows that the anhydroribose possesses one of the structures (II), (III), and (IV). No convenient method of distinguishing between these structures is at present available but the formation of either (III) or (IV) from 1 : 2 : 3-triacetyl 5-trityl ribose would involve an interchange of furanose and pyranose forms, which although not impossible, is not suggested by any evidence so far obtained. We therefore consider that our anhydroribose is 1 : 5′-5 : 1′-diribofuranose anhydride (II). The configurations at the glycosidic centres of the two ribose residues are not known, but it seems possible that the discrepancy between the rotations of our material and that of Bredereck, Köthnig, and Berger is due to isomerism at these positions.

Experimental.

Acetyl groups were determined by Alicino's method (*Analyt. Chem.*, 1948, **20**, 590).

1 : 2 : 3-*Triacetyl* 5-*Trityl* D-*Ribofuranose*.—(*a*) 5-Trityl D-ribose was acetylated following the method of Bredereck *et al.* (*loc. cit.*) (Found : OAc, 25·0. Calc. for $C_{26}H_{26}O_5$: OAc, 24·9%).

(*b*) A solution of D-ribose (11·6 g.), dried in a vacuum over phosphoric oxide at 60°, and trityl chloride (21·6 g.) in pyridine (116 c.c.), distilled three times from phosphoric oxide, was maintained at 37° for 4 days, with the exclusion of moisture, and then, after being heated at 70° for 30 minutes, was cooled to 5°, and acetic anhydride (60 c.c.) and anhydrous pyridine (50 c.c.) were added. The solution was set aside for a further 24 hours and was then poured into ice-water (3 l.) containing one drop of saturated aqueous trisodium phosphate. This assisted the coagulation of the precipitate which, after 30 minutes, was collected by filtration and purified as described by Bredereck *et al.* (*loc. cit.*) (Found : C, 71·8; H, 5·8; OAc, 22·8. Calc. for $C_{26}H_{26}O_5$: C, 69·5; H, 5·8; OAc, 24·9%). The yield (30 g.) of this material was approx. three times that obtained by using the method of the German workers, and although it probably contained a small quantity of triphenylmethyl acetate it was quite satisfactory for subsequent experiments, contamination being removed as triphenylmethyl bromide.

*Tetra-acetyl Di-*D*-ribose Anhydride*.—1 : 2 : 3-Triacetyl 5-trityl D-ribofuranose, prepared by either method, yielded by use of the procedure of the German workers, tetra-acetyl di-D-ribose anhydride in the form of needles, m. p. 168·5—169·5° [Found : C, 50·0; H, 5·5; OAc, 39·6%; *M* (cryoscopic in benzene), 428. Calc. for $C_{18}H_{24}O_{13}$: C, 50·0; H, 5·6. OAc, 39·8%; *M*, 432·2]. This material (62·1 mg.) was heated at 97° with N/10-hydrochloric acid (3 c.c.) for 165 minutes by which time the solution had $[\alpha]_D^{18}$ −21·6° (calculated on the assumption of the presence of D-ribose), unchanged on further heating. Under similar conditions D-ribose had $[\alpha]_D^{18}$ −21·2°. The solution obtained from the above hydrolysis was examined on the paper chromatogram alongside a specimen of authentic D-ribose, following Partridge's method (*loc. cit.*), an R_F value of 0·23 being obtained in each case. Partridge records a value of 0·21 for D-ribose.

*Di-*D*-ribose Anhydride*.—Tetra-acetyl di-D-ribose anhydride was deacetylated as described by Bredereck *et al.* (*loc. cit.*) and gave di-D-ribose anhydride in the form of colourless plates, m. p. 229° after sintering from 224° [Found : C, 45·7; H, 5·8%; *M* (cryoscopic in water), 246. Calc. for $C_{10}H_{18}O_8$: C, 45·5; H, 6·1%; *M*, 264]. In water the material had $[\alpha]_D^{18}$ +11° (*c*, 0·68). After 24 hours at 28° the compound had consumed 1·01 mols. of sodium metaperiodate, no formic acid being detected by titration with N/100-sodium hydroxide after destruction of periodate ions. The solution obtained after completion of this oxidation had $[\alpha]_D^{18}$ −48°, calculated on the assumed presence of 2 : 4-diformyldioxolan.

*Tetramethyl Di-*D*-ribose Anhydride*.—Tetra-acetyl di-D-ribose anhydride (0·091 g.) in acetone (10 c.c.) was stirred at 55°, and methyl sulphate (3·2 c.c.) and aqueous sodium hydroxide (8·6 c.c.; 30%) were added portionwise every 15 minutes during 2·5 hours. Further portions of acetone (5 c.c.) were added to aid mixing. Water (4 c.c.) was added and, after the temperature had been allowed to rise to 75° for 5 minutes, the reaction mixture was cooled to room temperature and extracted 12 times with chloroform (20 c.c. each). The combined chloroform extracts were dried ($MgSO_4$) and after distillation of the solvent the residual syrupy *tetramethyl di-*D*-ribose anhydride* crystallised when kept at 0°. It separated from light petroleum (b. p. 80—100°) in needles and plates (0·045 g.), m. p. 129·5—130° after sintering at 125° (Found : C, 52·9; H, 7·3; OMe, 37·4. $C_{14}H_{24}O_8$ requires C, 52·5; H, 7·5; OMe, 38·7%). The compound did not reduce Fehling's solution.

*Examination of the Products of Hydrolysis of Tetramethyl Di-*D*-ribose Anhydride*.—Tetramethyl di-D-ribose anhydride (10 mg.) was heated at 97° with N/10-hydrochloric acid (2 c.c.) for 40 minutes. This treatment had been found in a preliminary experiment to bring about complete hydrolysis of the material as shown by measurements of reducing power using Somogyi's method (*J. Biol. Chem.*, 1926, **70**, 599). After removal of chloride ions by grinding with silver oxide and filtration, the solution was examined on the paper chromatogram by Partridge's method (*loc. cit.*). One component was observed having an R_F value of 0·55. A further sample of the tetramethyl compound (4·946 mg.) was hydrolysed as above, N-sodium hydrogen carbonate (10 c.c.) and potassium periodate (6 c.c. of a 2·3% solution in N/3-sulphuric acid at 45°) were added (the pH of the solution was then 7·5), and the solution was set aside at room temperature for 24 hours. After destruction of excess of periodate ions, formaldehyde was determined by Jeanloz's method (*loc. cit.*). The formaldehyde–dimedon complex (2·03 mg.) had m. p. 188—190° alone or mixed with an authentic specimen. A third sample of tetramethyl di-D-ribose anhydride (4·076 mg.) was hydrolysed as before, and, after being kept with sodium metaperiodate for

50 hours at room temperature, no liberation of formic acid could be detected using the method of Halsall Hirst, and Jones (*J.*, 1947, 1427).

One of us (M. V. L.) thanks the Department of Scientific and Industrial Research for the award of a maintenance grant.

THE UNIVERSITY, MANCHESTER, 13. [*Received, August 12th*, 1949.]

7. *The Structure of Diallyl Disulphide.*

By FREDERICK CHALLENGER and DOUGLAS GREENWOOD.

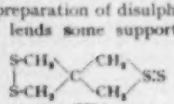
Diallyl disulphide reacts with triphenylphosphine yielding triphenylphosphine sulphide and diallyl monosulphide, with zinc yielding zinc sulphide and diallyl monosulphide, and with phenyl isocyanide, followed by aniline, yielding s-diphenylthiourea. These reactions are explained by a free-radical mechanism involving the intermediate compounds $Ph_3P(S{\cdot}C_3H_5)_2$, $Zn(S{\cdot}C_3H_5)_2$, and $Ph{\cdot}N{:}C(S{\cdot}C_3H_5)_2$, which were, however, not isolated.

An alternative explanation, assuming a branched-chain structure $R_2S{:}S$ for diallyl disulphide, is disproved by a reaction with cysteine whereby cystine and prop-2-ene-1-thiol are obtained in good yield. Dimethyl, diethyl, and di-*p*-nitrophenyl disulphide also react in this way with cysteine. Dimethyl and diethyl disulphide do not react with zinc or triphenylphosphine.

SEMMLER (*Arch. Pharm.*, 1892, **230**, 434) isolated diallyl disulphide from oil of garlic and found that on distillation with zinc dust it yielded diallyl monosulphide. He recorded no experimental details but we have confirmed his result. To explain this, it could be assumed that diallyl disulphide had a branched-chain structure (I) rather than the normal straight-chain structure (II).

(I.) $CH_2{:}CH{\cdot}CH_2{\cdot}S\underset{S}{\overset{}{\diagdown\diagup}}CH_2{\cdot}CH{:}CH_2$ $\qquad$ $CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}CH_2{\cdot}CH{:}CH_2$ (II.)

The preparation of disulphides of type (I) by Backer and Evenhuis (*Rec. Trav. chim.*, 1937, **56**, 129) lends some support to this view: tetrakisbromomethylmethane and sodium or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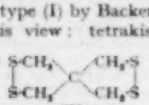
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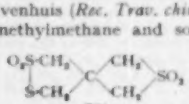
(V.)

potassium disulphide in alcohol give product (III) instead of the expected (IV); one atom of sulphur was removable by the action of sodium, copper, or sodium sulphide leaving the compound $C_5H_8S_2$, or by oxidation giving sulphuric acid and a disulphone (V) or the derived disulphonic acid $(HO_3S{\cdot}CH_2)_2C\langle^{CH_2}_{CH_2}\rangle SO_2$ according to conditions.

Cavallito, Buck, and Suter (*J. Amer. Chem. Soc.*, 1944, **66**, 1952) regarded the naturally occurring antibacterial substance allicin as $CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}S(\rightarrow O){\cdot}CH_2{\cdot}CH{:}CH_2$ or $CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}O{\cdot}S{\cdot}CH_2{\cdot}CH{:}CH_2$. Small, Bailey, and Cavallito (*ibid.*, 1947, **69**, 1710) and Stoll and Seebeck (*Helv. Chim. Acta*, 1948, **31**, 189) concluded from a comparison of chemical and antibacterial properties that allicin was also obtained by the direct oxidation of diallyl disulphide with perbenzoic acid or hydrogen peroxide. This favours the structure (II) rather than the branched-chain (I).

It seemed possible that diallyl disulphide could have structure (II) and yet react with zinc as stated by Semmler, if dissociation into free radicals were assumed :

$$C_3H_5{\cdot}S{\cdot}S{\cdot}C_3H_5 \rightleftharpoons 2C_3H_5{\cdot}S\cdot \xrightarrow{Zn} Zn(S{\cdot}C_3H_5)_2 \longrightarrow ZnS + (C_3H_5)_2S.$$

Such a reaction would be analogous with those observed by Schönberg, Rupp, and Gumlich (*Ber.*, 1933, **66**, 1932) with di(thio-α-naphthoyl) disulphide and metallic zinc or silver. We find that *bisallylthiozinc* cannot be isolated from the reaction between zinc and diallyl disulphide, but it has been prepared and found to decompose in the manner shown at temperatures (80—100°) much below those at which the reaction was carried out (120—130°).

It was therefore decided to investigate certain reactions of diallyl disulphide, which should enable a decision to be reached between structures (I) and (II).

We have recently (*Biochem. J.*, 1949, **44**, 87) shown that diallyl disulphide in cultures of the

mould *Scopulariopsis brevicaulis* yields prop-2-ene-1-thiol and methyl allyl sulphide, thus behaving in the same way as saturated alkyl disulphides (Challenger *et al.*, *J.*, **1937**, 868; **1938**, 1872). This favours structure (II). On the alternative structure (I), the formation of hydrogen sulphide and allyl sulphide would be expected, but this was not observed. Moreover, diallyl monosulphide yields no prop-2-ene-1-thiol in cultures of *S. brevicaulis*, but volatilises apparently unchanged, as does also diethyl sulphide (Challenger and North, *J.*, **1934**, 70; North, Thesis, Leeds, **1933**). The formation of the thiol and methyl allyl sulphide from the disulphide in mould cultures cannot therefore be explained by the further breakdown of diallyl monosulphide formed as an intermediate compound from a disulphide of structure (I).

Schönberg (*Ber.*, **1945**, **68**, 162) used triphenylphosphine for the detection of free radicals arising from disulphides by homolytic fission. Later, in a private communication (cf. this vol., pp. 892, 889), Schönberg classified disulphides into two groups, according to their reaction with triphenylphosphine: (1) unreactive, *e.g.*, diethyl and dibenzyl disulphide, and (2) those reacting to give Ph_3PS, probably by way of $Ph_3P(SR)_2$, *e.g.*, di-(*p*-dimethylaminophenyl) and dibenzoyl disulphide.

Some disulphides, *e.g.*, Ph_2S_2, oxidise triphenylphosphine to triphenylphosphine oxide in presence of water, probably by way of the intermediate compound $Ph_3P(SR)_2$ which was not isolated.

$$R_2S_2 \rightleftharpoons 2R{\cdot}S^- \xrightarrow{Ph_3P} Ph_3P(SR)_2 \xrightarrow{H_2O} Ph_3PO + 2R{\cdot}SH$$

The disulphide was often regenerated from the resulting thiol by the oxygen of the air. The reactions of compounds of class 2 recall the formation of triphenylphosphine sulphide from triphenylphosphine and dithiocyanogen, doubtless through the unstable $Ph_3P(SCN)_2$ (Challenger, Smith, and Paton, *J.*, **1933**, 1055).

We find that diallyl disulphide with triphenylphosphine at 80—90° with or without water gives triphenylphosphine sulphide in good yield, and therefore falls into group 2. Diallyl monosulphide was also formed and was characterised in one experiment as the *sulphilimine*.

Schönberg (*loc. cit.*) showed that certain disulphides of group 2 did not react with phenyl *iso*cyanide in conditions where elementary sulphur would form phenyl *iso*thiocyanate. He therefore concluded that Ph_3PS arose from $Ph_3P(SR)_2$ and not from free sulphur formed in solution by dissociation of a disulphide to a monosulphide and sulphur. However, with diallyl disulphide we obtained evidence of the formation of phenyl *iso*thiocyanate, *s*-diphenylthiourea being obtained after reaction with aniline. This appears to favour formula (I); yet the free radicals of diallyl disulphide might be more reactive than those of the disulphides tested by Schönberg, and might react to give $PhN{:}C(S{\cdot}C_3H_5)_2$ (VI). This could then (*a*) break down directly to allyl monosulphide and phenyl *iso*thiocyanate which, with aniline, would give the thiourea or (*b*) (VI) might itself react with aniline thus:

$$PhN{:}C(S{\cdot}C_3H_5)_2 + NH_2Ph \longrightarrow (Ph{\cdot}NH)_2C(S{\cdot}C_3H_5)_2 \longrightarrow (C_3H_5)_2S + CS(NHPh)_2$$

Scheme (*a*) is perhaps more likely because of the ease with which most compounds of the type $X(S{\cdot}C_3H_5)_2$ (where X is, *e.g.*, a metal or Ph_3P) break down to XS and allyl sulphide. However, if either of the above schemes is correct, it renders this reaction useless for distinguishing between a free-radical mechanism and formation of elementary sulphur.

Triphenylstibine, although less reactive than triphenylphosphine, gives compounds which are more stable than those of triphenylphosphine (Challenger and Wilson, *J.*, **1927**, 209). No reaction occurred between triphenylstibine and diallyl disulphide.

The symmetrical structure (II) for diallyl disulphide is supported by the work of Koch (*J.*, **1949**, 394) on the ultra-violet absorption spectra of disulphides and has now been established by the reaction of diallyl disulphide with cysteine yielding cystine and prop-2-ene-1-thiol in over 90% yield. If diallyl disulphide had structure (I), it would be impossible to explain this reaction: production of hydrogen sulphide might be expected (no trace of this was detected), and any further reduction could not by any mechanism yield over 50% of the thiol. For structure (II), the reaction appears as a normal reductive fission of a disulphide, accompanied by oxidation of cysteine to cystine. Cysteine seems not to have been used as a reducing agent for simple disulphides, although Harrison (*Biochem. J.*, **1927**, **21**, 1408) found that the oxidation of cysteine, by the oxygen of the air and by methylene blue, is catalysed by biscarboxymethyl disulphide; the activity disappeared if the disulphide link were destroyed, *e.g.*, by oxidation with bromine. Bersin and Steudel (*Ber.*, **1938**, **71**, 1015) found that cysteine and biscarboxymethyl disulphide come to a 50% equilibrium with cystine and thioglycollic acid in aqueous solution. We found this type of reaction to occur also with dimethyl disulphide which gave methanethiol and

cystine in 97% yield; diethyl and di-*n*-butyl disulphide required heat and gave lower yields, and a slow decomposition of the cysteine yielded hydrogen sulphide (for a similar decomposition of cysteine in aqueous solution see Mörner, *Z. physiol. Chem.*, 1904, **42**, 354, and Routh *J. Biol. Chem.*, 1939, **180**, 297). Di-*p*-nitrophenyl disulphide also yields the thiol and cystine.

Dimethyl and diethyl disulphide did not react with triphenylphosphine (cf. Schönberg, *loc. cit.*). They reacted hardly at all with zinc, even when heated, in contrast to statements that alkyl disulphides yield bisalkylthiozinc (Richter, "Organische Chemie," 11th edn., 1909, Vol. I, p. 162; Houben, "Die Methoden der Organischen Chemie," 1922, Vol. II, p. 365).

Addendum.

It seemed possible that, in a high-boiling solvent and in absence of moisture (see p. 27), triphenylphosphine sulphide might also be formed from the phosphine and diphenyl disulphide. We failed to find any. In mesitylene or in nitrobenzene the phosphine oxide, but no sulphide, was isolated. We then found that in these solvents or in "liquid paraffin," but not in benzene, at the b. p. in presence of air the oxide is formed even in absence of diphenyl disulphide. From the phosphine and diphenyl disulphide in boiling mesitylene in absence of moisture and under nitrogen, neither the oxide nor the sulphide was obtained, although some triphenylphosphine oxide was formed when the reaction mixture was then left in contact with air at room temperature. In a private communication (27th May, 1949) Professor Schönberg states that he has observed independently that "triphenylphosphine reacts with the oxygen of the air at high temperatures, especially in the presence of light."

Schönberg *et al.* (*loc. cit.*) consider that several reactions of disulphides are best explained on the assumption of a homolytic dissociation into free radicals, *e.g.*, the action of metals and of triphenylmethyl giving RS·Metal and R·S·CPh_3, and the observation that certain disulphides do not obey Beer's dilution law. Waters ("Free Radicals," Oxford Univ. Press, 1946, pp. 72—73) accepts this free-radical mechanism.

The authors adopted this view in the present paper. A Referee has, however, suggested an alternative explanation of the reaction with triphenylphosphine. Polarisation of R_2S_2, thus $\overset{+}{R}S\overset{\curvearrowright}{-}\overset{-}{S}R$, might lead to fission, the positive moiety being captured by the unshared electrons of the phosphorus to give the salt-like product $[Ph_3\overset{+}{P}{\cdot}SR]\overset{-}{S}R$. This could then break down to Ph_3PS and R_2S (allyl sulphide) and with water would yield Ph_3PO and RSH. This, it was remarked, would be in accord with the accepted mechanism for the hydrolysis of the *iso*cyanides by acids.

We accept this as an alternative representation of the reaction; the ionisation of a disulphide and the capture of a positive methyl group by the unshared electrons of an arsenic or selenium atom were, in fact, suggested by one of us in earlier discussions of the mechanism of biological methylation (Challenger, Taylor, and Taylor, *J.*, 1942, 49; Challenger, *Chem. and Ind.*, 1942, **61**, 414; *Chem. Reviews*, 1945, **36**, 342). Similar considerations apply to the reaction between phenyl *iso*cyanide and diallyl disulphide.

Experimental.

Diallyl Monosulphide and Scopulariopsis brevicaulis *in Bread Cultures.*—Four 1-l. flasks, each containing 150 g. of bread-crumbs and 25 c.c. of distilled water, were sterilised at 120°, inoculated with spores from a potato–agar subculture of *S. brevicaulis*, and incubated for 6 days at 32° and for 3 days at room temperature. Diallyl monosulphide (0·25 g.), emulsified with 25 c.c. of sterile water, was then added with a sterile pipette to each flask. The flasks were connected in series by means of sterile rubber bungs and glass tubing, and sterile air passed through them, for 18 days, into 2 tubes containing 4% aqueous mercuric cyanide and 5 tubes containing 3% aqueous mercuric chloride. No precipitate formed in either of the cyanide tubes, but a white precipitate was produced in all the chloride tubes during the first 18 days. The white precipitate (3·8 g.) did not melt below 260°, but darkened and sintered above 190°. It was insoluble in the common organic solvents, and gave mercuric oxide with cold sodium hydroxide solution, and the odour of allyl sulphide with 6*N*-hydrochloric acid. The precipitate was thus the mercurichloride of allyl sulphide which had volatilised unchanged from the cultures.

Diallyl Disulphide.—Our sample of this compound (*Biochem. J.*, 1949, **44**, 90) (Found: C, 49·8; H, 7·23; S, 43·1. Calc. for $C_6H_{10}S_2$: C, 49·3; H, 6·85; S, 43·8%) apparently contained a trace of the monosulphide. The absence of thiol was shown by shaking with 4% mercuric cyanide solution, no precipitate being formed.

Diallyl Disulphide and Zinc.—5·0 G. of diallyl disulphide and 2·5 g. (slight excess) of zinc dust were mixed, and left at room temperature for 3 days. There was no change in odour or appearance after this time, or after maintaining the mixture at 60° for 2 hours and then at 100° for 2 hours. After 10 hours at 120—130°, the odour of disulphide was almost completely replaced by that of allyl monosulphide. The

oil was then decanted from the zinc dust, and fractionated at 16 mm., giving (i) an almost colourless oil, b. p. 35—45° (2 c.c.), having the odour of allyl monosulphide (b. p. 40°/16 mm.), and (ii) an orange-red oil, b. p. 60—85° (2·5 c.c.), probably mainly unchanged diallyl disulphide (b. p. 78—80°/16 mm.). The first fraction was redistilled at 16 mm., a fraction being collected between 36° and 40°. Two drops of this were shaken with saturated chloramine-T solution. The precipitate, when separated and recrystallised from ethyl acetate–ligroin (b. p. 40—60°), had m. p. and mixed m. p. with authentic diallyl sulphilimine, 71°.

The zinc dust was only slightly changed in appearance, being slightly darker and coarser than previously. Addition of hydrochloric acid gave hydrogen sulphide, but no odour of a thiol. The product therefore contained zinc sulphide.

Bisallylthiozinc.—A few drops of prop-2-ene-1 thiol, shaken with excess of zinc acetate solution, gave immediately *bisallylthiozinc* as a white precipitate. This was separated after 30 minutes. It sintered from 120° to 200°. It was insoluble in the common organic solvents and was therefore purified by washing it with large quantities of water, alcohol, and ether (Found: Zn, 30·4. $C_6H_{10}S_2Zn$ requires Zn, 30·9%).

When it was refluxed with benzene for 10 minutes, decomposition occurred. The residual pale yellow powder on treatment with dilute hydrochloric acid gave the odour of hydrogen sulphide with only a very slight odour of thiol; it was unmelted below 270°, but showed a colour change at 200—220° characteristic of zinc sulphide.

The same decomposition was observed with dry bisallylthiozinc at 100°. The odour of allyl sulphide was noticed after 15 minutes. The product was extracted with a little alcohol, and the solution added to a saturated solution of chloramine-T, giving a crystalline precipitate, m. p. 70°. The mixed m. p. with authentic allyl sulphilimine was 71°. The residue, insoluble in alcohol, gave no odour of a thiol with dilute hydrochloric acid.

Allyl Sulphilimine.—13·6 g. of chloramine-T in about 200 c.c. of water, and 6 g. of diallyl monosulphide were shaken for 20 minutes. The product, which formed within a few seconds, was separated, dried, and recrystallised by addition of light petroleum (b. p. 40—60°) drop by drop to a solution in chloroform. After 3 such recrystallisations, the *sulphilimine* had the constant m. p. 72° (Found: C, 54·8; H, 6·1; N, 5·1. $C_{13}H_{17}O_2NS_2$ requires C, 55·1; H, 6·0; N, 5·4). It is converted into an oil on storage at room temperature for 3—4 days, or rapidly at 100°. At 0° the sulphilimine is stable for 3—4 weeks. No loss in weight is involved. The nature of this change will form the subject of a further communication.

Reaction of Dimethyl and Diethyl Disulphide with Zinc.—Heating dimethyl disulphide (10 hours at 100—110°) or diethyl disulphide (9 hours at 130°) with zinc, yielded no monosulphide, almost all the disulphide being recovered unchanged. Traces of $Zn(SR)_2$ were detected in each reaction by the slight odour of a thiol produced on addition of hydrochloric acid.

Diallyl Disulphide and Triphenylphosphine.—The disulphide (0·3 g.), triphenylphosphine (0·5 g.), and benzene (4 c.c.) were refluxed for 6 hours in the absence of water. On cooling, triphenylphosphine sulphide (0·4 g.) separated (m. p. and mixed m. p. 161—162°). The benzene solution was distilled, with addition of fresh benzene to the residue, until the odour of allyl sulphide had passed entirely into the distillate. This was then shaken for 45 minutes with an aqueous solution of chloramine-T to form the sulphilimine. Evaporation of the benzene at room temperature left a white solid which, when recrystallised once from chloroform–ligroin, had m. p. and mixed m. p. with allyl sulphilimine, 71°. Repetition of this experiment in toluene at 90° in presence of water again gave triphenylphosphine sulphide, m. p. 162—163° (161—162° on admixture with an authentic specimen, m. p. 161—162°). The m. p. of triphenylphosphine oxide (151°) was depressed to 123°.

Diphenyl Disulphide and Triphenylphosphine.—Triphenylphosphine (1 g.) was heated in boiling nitrobenzene (7 c.c.) for 6 hours. Evaporation then left a tarry residue, which on extraction with ligroin (b. p. 80—100°) for 1 hour and recrystallisation from benzene–ligroin yielded triphenylphosphine oxide (0·3 g.), m. p. 153—154° (mixed m. p. 154°).

The phosphine (0·2 g.) was heated in boiling mesitylene (2 c.c.) for 5 hours with precautions to exclude moisture from the apparatus. Cooling and addition of ligroin (b. p. 40—60°) gave 0·08 g. of the phosphine oxide, m. p. and mixed m. p. 156°.

The phosphine (0·5 g.), diphenyl disulphide (0·42 g.), and mesitylene (5 c.c.) (all dried over P_2O_5; the mesitylene then redistilled) were refluxed for 6 hours in a dried apparatus in a stream of nitrogen previously passed through alkaline pyrogallol, sulphuric acid, and phosphoric oxide. On cooling and addition of ligroin to a portion, no crystals appeared, showing that no phosphine oxide or sulphide had been formed. However, after storage in air in a closed flask for 10 days, addition of ligroin gave 0·12 g. of the phosphine oxide, m. p. 154° (mixed m. p. 153°). Distillation of the solvents in a stream of nitrogen left a red liquid residue, which when kept overnight in air and then treated with ligroin gave a further 0·13 g. of the phosphine oxide. The residue after evaporation of the ligroin slowly deposited diphenyl disulphide, m. p. and mixed m. p. 60°.

Diallyl Disulphide and Phenyl iso*Cyanide* (Experimental conditions were obtained from a private communication from Professor A. Schönberg).—Diallyl disulphide (3 g.), phenyl *iso*cyanide (2 g.; b. p. 64°/20 mm.) and benzene (25 c.c.) were refluxed for 8 hours. Aniline (2 g.) was then added, and refluxing continued for a further 3 hours, a colour change from bluish-green to orange-red being then observed. Orange crystals separated overnight and were removed and washed with cold benzene and ether. After recrystallisation from alcohol, the product (0·65 g.) had m. p. 153° alone and mixed with authentic *s*-diphenylthiourea. The benzene mother-liquor was washed with concentrated hydrochloric acid (to remove aniline and phenyl isocyanide) and with water, dried (Na_2SO_4), and evaporated at 40—50 mm., giving a further quantity of orange solid and unchanged diallyl disulphide.

Diallyl Disulphide and Triphenylstibine.—The disulphide (1·0 g.) and triphenylstibine (2·5 g.) in ligroin (b. p. 80—100°; 50 c.c.) were refluxed for 30 hours. There was no reaction.

When twice these quantities were used without a solvent during 3 hours at 100° and 8 hours at 140°, a viscous liquid slowly formed; no solid product was isolated.

Diallyl Disulphide and Cysteine.—Cysteine hydrochloride (1·0 g.) in water (*ca.* 15 c.c.) was neutralised with 10% sodium hydrogen carbonate solution (*ca.* 5 c.c.), and diallyl disulphide (0·167 g.) added. After

56 hours at room temperature in a stream of nitrogen the reaction was complete. The nitrogen, with the volatile products, passed through 2 tubes containing 4% aqueous mercuric cyanide to absorb thiols, and 3 tubes containing 3% aqueous mercuric chloride to absorb unchanged disulphide. Bisallylthiomercury (0·358 g.), m. p. and mixed m. p. 72°, was obtained from the first cyanide tube. This represents 0·152 g. (91%) of diallyl disulphide. The white precipitate (0·097 g.) in the mercuric chloride tubes had the properties expected of a mercurated fission product of diallyl disulphide. It gave an odour of a thiol with hydrochloric acid and a precipitate of mercuric oxide with sodium hydroxide solution, and was unmelted below 270° (*Biochem. J.*, 1949, **44**, 89). It represented about 0·016 g. (10%) of diallyl disulphide. Experimentally, 1 g. of diallyl disulphide gives about 6 g. of mercuric chloride derivative.

Cystine (0·25 g.) was removed from the reaction flask. Alone and in admixture with authentic cystine its m. p. (decomp.) was 256—258°. It was equivalent to 0·153 g. or 91·5% of the disulphide used.

Dimethyl Disulphide and Cysteine.—0·078 G. of dimethyl disulphide and excess of cysteine hydrochloride solution (1 g. in *ca.* 15 c.c.), neutralised as before, were left in a stream of nitrogen, as in the previous experiment.

Bismethylthiomercury (0·238 g., 97·5%) was obtained from the first cyanide tube. After one recrystallisation from ethyl acetate, it had m. p. and mixed m. p. 174°. A trace of precipitate in the chloride tubes probably accounted for the remaining 2·5% as unchanged disulphide. Cystine (0·196 g., equivalent to 98% of the disulphide) was recovered.

Diethyl Disulphide and Cysteine.—The reaction was slow. The disulphide (0·074 g.) and cysteine hydrochloride (0·5 g.), neutralised as before, were heated at 100° in nitrogen for 2½ hours. The precipitate in the first cyanide tube contained a trace of mercuric sulphide and was purified by decomposing it with 70% hydrochloric acid, and aspirating the gas again into mercuric cyanide solution, followed by recrystallisation from alcohol. The bisethylthiomercury (0·034 g., representing 17% of the disulphide used) melted at 75° (76° on admixture with an authentic specimen). The cystine formed had m. p. and mixed m. p. 256° (decomp.).

Di-n-butyl Disulphide and Cysteine.—The disulphide (0·05 g.), cysteine hydrochloride (1·0 g.), and 3·5% sodium hydrogen carbonate solution (*ca.* 15 c.c.) were heated for 11 hours at 100° in nitrogen. The greenish-black precipitate (0·266 g.) from the mercuric cyanide gave scarcely any thiol with hydrochloric acid, and was insoluble in hot alcohol. It was mainly mercuric sulphide and as the quantity was so large, decomposition of the cysteine was suspected. Cysteine hydrochloride and aqueous sodium hydrogen carbonate evolved hydrogen sulphide slowly at 100°, and mercuric sulphide was gradually precipitated in the mercuric cyanide.

Di-p-nitrophenyl Disulphide and Cysteine.—The disulphide (0·5 g.; m. p. 181—182°; Willgerodt, *Ber.*, 1885, **18**, 331, gives m. p. 180—181°; Fromm and Wittmann, *ibid.*, 1908, **41**, 2264, give m. p. 182°) and cysteine hydrochloride (0·5 g.), neutralised with sodium hydrogen carbonate, were refluxed in 50% aqueous alcohol for 2½ hours, cooled, and poured into excess of dilute hydrochloric acid, thus precipitating the *p*-nitrothiophenol and any unchanged disulphide. The precipitate sintered without complete fusion at 76°. It was dissolved in dilute sodium hydroxide, filtered from a small amount of disulphide, and reprecipitated by dilute hydrochloric acid. When quickly dried, it had m. p. 77° (the recorded m. p. of *p*-nitrothiophenol; Willgerodt, *loc. cit.*; Fromm and Wittmann, *loc. cit.*) but was rapidly re-oxidised to the disulphide.

The cystine was recovered by neutralising the acid solution with sodium hydrogen carbonate. It had m. p. 252° (decomp.) alone or mixed with an authentic cystine.

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THE UNIVERSITY, LEEDS. [*Received, August 20th*, 1949.]

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8. *Derivatives of Oxazolid-2 : 4-dione. Part I. The Alkylation of 5 : 5-Dimethyloxazolid-2 : 4-dione.**

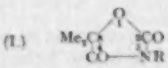
By J. S. H. DAVIES and W. H. HOOK.

A number of *N*- and *O*-alkyl derivatives of 5 : 5-dimethyloxazolid-2 : 4-dione has been prepared. The *O*-alkyl derivatives are shown to be 4-enol ethers and have been isomerised to the corresponding *N*-alkyl derivatives. The hydrolysis products of the *N*-alkyl derivatives have been studied.

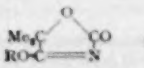
N-ALKYL derivatives of oxazolid-2 : 4-diones have been described by Ahlqvist (*J. pr. Chem.*, 1919, **99**, 77), who obtained 3-ethyloxazolid-2 : 4-dione by the hydrolytic desulphurisation of 2-thio-3-ethyloxazolid-4-one, and by Spielman (*J. Amer. Chem. Soc.*, 1944, **66**, 1244; cf. B.P. 561,183), who prepared 3-methyl derivatives of oxazolid-2 : 4-diones, having lower alkyl groups in the 5-position, by treating an aqueous alkaline solution of the appropriate oxazolid-dione with methyl sulphate. According to Spielman, methylation gave poor yields, and ethylation with

* Patents pending.

ethyl sulphate failed. The preparation of 5 : 5-*dimethyl*-3-*ethyloxazolid*-2 : 4-*dione* (I; R = Et) by a modified procedure (anhydrous conditions) was reported in a preliminary communication (*Nature*, 1947, **160**, 610) and is more fully described below. It has since been possible to show that ethylation is effected to a limited extent by Spielman's aqueous alkylation procedure when reaction is prolonged (72 hours).



(I.)



(II.)

By treatment of the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione with ethyl iodide Spielman (*loc. cit.*) obtained a compound, m. p. 61—62°, which he considered to be 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. In contrast to the 3-methyl derivative, his product has now been shown to be unstable to dilute aqueous mineral acid which yields the original dione, and to aqueous alkali which yields the sodium salt of the dione. With ammonia in dry ethanol, it forms an *imino*-derivative, which is also hydrolysed by boiling hydrochloric acid to the original dione. This imino-derivative is not identical with 2-*imino*-5 : 5-*dimethyloxazolid*-4-*one* prepared by condensation of ethyl α-hydroxyisobutyrate with guanidine (cf. Traube and Ascher, *Ber.*, 1913, **46**, 2077). Spielman's product is, therefore, now regarded as the 4-enol ethyl ether, *i.e.*, 4-*ethoxy*-5 : 5-*dimethyloxazol*-2-*one* (II; R = Et). 4-*Methoxy*- and 4-*benzyloxy*-5 : 5-*dimethyloxazol*-2-*one* have also been prepared by Spielman's method. These enol ethers slowly isomerise when heated at 180°, alone or in the presence of the alkyl halide, to the *N*-alkyl derivatives identical with the products prepared as described below. If the alkyl group of the halide differs from that of the *O*-alkyl derivative, exchange occurs. Thus, the *O*-ethyl derivative is converted by methyl iodide at 180° into the *N*-methyl derivative, and benzyl bromide similarly furnishes the *N*-benzyl derivative.

Although *O*-alkylation is the preponderating reaction between the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione and ethyl iodide at room temperature, an increasing amount of the *N*-ethyl derivative is formed as the temperature is raised. After 3 days in ether at room temperature, the product contains some 10% of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, whilst after 2 hours in boiling toluene 30% of this derivative is obtained. Work so far carried out suggests that the *O*-ethyl derivative is not necessarily an intermediate in the formation of the *N*-ethyl compound from the silver salt.

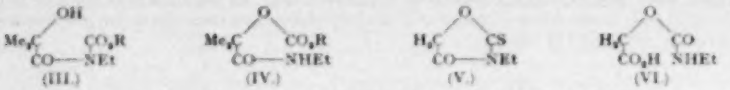
In view of the importance of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione (I; R = Me) in the treatment of "petit mal," myoclonic and akinetic epilepsies (Lennox, *J. Amer. Med. Assoc.*, 1945, **129**, 1069), improved methods for the alkylation of oxazolid-2 : 4-diones have been worked out, and new *N*-alkyl derivatives have been prepared for pharmacological investigation.

N-Alkylation of 5-substituted oxazolid-2 : 4-diones has now been found to proceed more readily and in good yield when the sodium or potassium salts are treated with an alkyl sulphate or halide under anhydrous conditions. Thus, when 5 : 5-dimethyloxazolid-2 : 4-dione in dry ethanol is treated first with sodium ethoxide and then with ethyl sulphate, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, m. p. 76—77°, is formed almost quantitatively, and this product is chemically similar to Spielman's 3-methyl derivative. Alternatively, alkylation may be carried out in excellent yield in acetone solution containing anhydrous potassium carbonate. Some *N*-alkyl derivatives are most conveniently prepared directly from ethyl α-hydroxyisobutyrate in one stage. The hydroxy-ester is condensed with urea in the presence of sodium ethoxide (Stoughton, *J. Amer. Chem. Soc.*, 1941, **63**, 2376) to form the sodium salt of 5 : 5-dimethyloxazolid-2 : 4-dione, and use of this solution directly for alkylation has furnished the 3-*n*- and -iso-*propyl*, 3-n- and -iso-*butyl*, 3-n- and -iso-*amyl*, 3-*allyl*, 3-2′-*methylallyl*, and 3-*benzyl* derivatives.

The above methods have been extended to the introduction of substituted alkyl groups, the 3-2′-*hydroxyethyl*, 3-2′-*ethoxyethyl*, 3-2′-*methylthioethyl*, and 3-*acetoaceloxyethyl* derivatives having been thus prepared. 5 : 5-Dimethyl-3-2′-diethylaminoethyloxazolid-2 : 4-dione was very conveniently prepared from diethylaminoethyl chloride hydrochloride by the potassium carbonate–acetone method, the free base being liberated *in situ*.

N-Alkyloxazolid-2 : 4-diones are moderately stable to mineral acids, but are rapidly hydrolysed by aqueous sodium hydroxide, a reaction which is used as a method of assay (Spielman, *loc. cit.*). This hydrolysis, however, gives rise to two products—*sodium* N-α-*hydroxyisobutyryl*-N-*ethylcarbamate* (III; R = Na) and 1-(*ethylcarbamyl*)*isopropyl carbonate* (IV; R = Na). Acidification of the hydrolysis mixture causes decarboxylation of the latter to the hydroxyamide, whereas it is possible to isolate the free carbamic acid, which is fairly stable and may be deter-

mined in the solution by titration. Utilising these facts, it has been observed that the proportion of lactone hydrolysis, giving rise to (III), increases with the complexity of the *N*-alkyl substituent.



(III.) (IV.) (V.) (VI.)

α-Hydroxyisobutyroethylamide, formed by decarboxylation of (IV; R = H) as above, is a low-melting solid, characterised as the 3 : 5-*dinitrobenzoate*. It is also formed when (III; R = H) decomposes on being melted. This latter decarboxylation is accompanied by partial cyclodehydration, yielding the original 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. Decarboxylation occurs to the extent of 75% when (III; R = H) is heated alone or with copper powder, but when an aqueous solution of the acid is boiled with copper powder this amount is increased to 88%; in all cases the remaining acid undergoes cyclisation. On storage in aqueous solution at room temperature, the acid slowly cyclises and 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione crystallises from the solution.

By alkaline hydrolysis of 2-thio-3-ethyloxazolid-4-one (V) and treatment of the product with bromine, Ahlqvist (*loc. cit.*) obtained a product, which he considered to be *N*-ethylcarbamylglycollic acid (carboxymethyl *N*-ethylcarbamate) (VI). Hydrolysis and desulphurisation, by the method of Ahlqvist, of 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one, the preparation of which is described in Part III (*J.*, 1950, **36**) also gives (III; R = H). It seems probable, therefore, that Ahlqvist's product is *N*-ethyl-*N*-glycollylcarbamic acid and not (VI).

In a publication which has appeared since the completion of this work, Spielman (*J. Amer. Chem. Soc.*, 1948, **60**, 1021) mentions the use of methanol as a solvent for the methylation procedure, the alkaline reagent presumably being sodium hydroxide as in his earlier experiments. He mentions also an alternative alkylation procedure, in which the potassium salt of the oxazolidione is first formed by treating the dione in "Cellosolve" with potassium hydroxide. In the present work, alkylation proceeded most efficiently under strictly anhydrous conditions, and alkali-metal hydroxides were better replaced by alkoxides in alcoholic solution or anhydrous potassium carbonate in non-hydroxylic solvents.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

O-Alkylation. 4-*Ethoxy*-5 : 5-*dimethyloxazol*-2-*one*.—In accordance with Spielman's procedure, a mixture of the dry silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione (60 g.), dry ether (400 c.c.), and ethyl iodide (50 g.) was set aside, with occasional shaking, at room temperature for 3 days. Filtration of the product and evaporation of the ether yielded a residue (22·4 g.), which was distilled. The fraction (10·4 g.), b. p. 90—91°/0·5 mm., partly solidified and was crystallised from dry ether, yielding a product (4·5 g.), m. p. 58—60°; recrystallisation raised the m. p. to 61—62°, which is that of the product described by Spielman and now considered to be 4-ethoxy-5 : 5-dimethyloxazol-2-one.

The total ether-soluble product (4·6 g.), obtained from 10 g. of silver salt as above was warmed with dilute hydrochloric acid for 15 minutes to convert the ethoxy-compound into 5 : 5-dimethyloxazolid-2 : 4-dione. The cooled mixture was made alkaline with sodium hydrogen carbonate to convert the latter into its sodium salt, and then extracted with ether. The ethereal extract yielded a crude residue (0·45 g.), which on crystallisation from ether afforded 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, identical with the product described below. Similarly, reaction of the silver salt (10 g.) with ethyl iodide in boiling toluene for 2 hours yielded a mixed product (4·5 g.), which after treatment with hydrochloric acid and sodium hydrogen carbonate afforded the crude 3-ethyl derivative (1·5 g.).

Reactions of 4-*Ethoxy*-5 : 5-*dimethyloxazol*-2-*one* (II; R = Et).—(*a*) Treatment with a slight excess of 2*N*-sodium hydroxide and back-titration with hydrochloric acid (phenolphthalein) gave equiv. = 155·7 (Calc., 157). Acidification of the liquors and ether-extraction yielded 5 : 5-dimethyloxazolid-2 : 4-dione. (*b*) Heating the ether alone in a sealed tube at 180° for 24 hours afforded, almost quantitatively, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. With ethyl iodide, conversion was almost complete after 18 hours at 180°, but only partial after 72 hours at 140°. (*c*) Heating the ether with methyl iodide at 180° for 18 hours yielded 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, and with benzyl bromide under similar conditions the 3-benzyl derivative (see below) was formed. (*d*) The *O*-ethyl compound (2·4 g.) in dry ethanol (20 c.c.) was treated with a stream of dry ammonia for 15 minutes. The ethanol was distilled off and the residue (2·2 g.) recrystallised from ethanol, 4-*imino*-5 : 5-*dimethyloxazolid*-2-*one* being obtained as fine colourless prisms, m. p. 270—271° (decomp.) (Found: C, 46·8; H, 6·5. $C_5H_8O_2N_2$ requires C, 46·9; H, 6·3%). When the imino-derivative was heated on a steam-bath for ½ hour with hydrochloric acid, ether-extraction of the resulting solution yielded 5 : 5-dimethyloxazolid-2 : 4-dione, m. p. 76—77°.

2-*Imino*-5 : 5-*dimethyloxazolid*-4-*one* was prepared by condensation of ethyl α-hydroxyisobutyrate with guanidine (cf. Traube and Ascher, *loc. cit.*). It crystallised from ethanol as colourless prisms, m. p. 245—246° (Found: C, 47·0; H, 6·4%). The mixed m. p. with the 4-imino-derivative was 200—210° (decomp.). The 2-imino-derivative was hydrolysed to 5 : 5-dimethyloxazolid-2 : 4-dione by heating it with hydrochloric acid.

4-*Methoxy*-5 : 5-*dimethyloxazol-2-one*.—The dry silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione in ethereal suspension was allowed to react with methyl iodide at room temperature for 3 days. Filtration and concentration of the ethereal solution yielded the 4-*methoxy*-derivative as fine colourless needles, m. p. 153—154°, sparingly soluble in ether (Found : C, 50·15; H, 6·2. $C_6H_9O_3N$ requires C, 50·35; H, 6·3%). It was isomerised to the 3-methyl derivative by heating it at 180° for 18 hours, and with alcoholic ammonia yielded 4-imino-5 : 5-dimethyloxazolid-2-one.

4-*Benzyloxy*-5 : 5-*dimethyloxazol-2-one*.—This *ether*, prepared similarly, by use of benzyl bromide, formed colourless needles, m. p. 147—148° (Found : N, 6·7. $C_{12}H_{13}O_3N$ requires N, 6·4%). When heated at 180° for 60 hours, it furnished the 3-benzyl analogue.

N-*Alkylations*.—The preparation of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione by method (*a*) below is typical of the *N*-alkylation procedure employed. For the introduction of higher alkyl groups the iodides were used, and for secondary halides or 2-substituted halides the time of reaction was longer. For *products* prepared see the table.

5 : 5-*Dimethyl*-3-*ethyloxazolid*-2 : 4-*dione*. (*a*) To a solution of sodium (4·6 g.) in dry ethanol (100 c.c.) were added dry urea (12 g.) and ethyl α-hydroxyisobutyrate (26·4 g.), prepared by the method of U.S.P. 2,349,795. The reaction mixture was refluxed for 16 hours, and dissolved ammonia then removed by drawing a current of dry air through the boiling solution. The mixture was treated dropwise, with stirring, with ethyl sulphate (30·8 g.) and then refluxed for 2 hours, and the ethanol removed by distillation. The residue was treated with iced water and extracted with ether, the extract dried, and the solvent was removed. 5 : 5-Dimethyl-3-ethyloxazolid-2 : 4-dione (21·5 g., 68·5%) crystallised from aqueous methanol as flat, vitreous prisms, m. p. 76—77° (Found : C, 53·7; H, 7·1. $C_7H_{11}O_3N$ requires C, 53·5; H, 7·1%).

(*b*) 5 : 5-Dimethyloxazolid-2 : 4-dione (25·8 g.) in dry acetone (200 c.c.) was stirred for 3 hours with anhydrous potassium carbonate (30 g.). Ethyl sulphate (30·8 g.) was added to the mixture, which was refluxed for 6 hours. After filtration from inorganic material, the product (27·5 g., 87%) was isolated by removal of solvent and working up as above.

(*c*) 5 : 5-Dimethyloxazolid-2 : 4-dione (12·9 g.) in a solution of sodium hydroxide (5 g.) in water (50 c.c.) was stirred vigorously at room temperature with ethyl sulphate (15·4 g.) for 72 hours. The crystalline solid which separated was crystallised from aqueous methanol, affording 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (3·1 g.) in 20% yield.

Hydrolysis of 5 : 5-*Dimethyl*-3-*alkyloxazolid*-2 : 4-*diones*.—(a) 3-*Ethyl derivative*. Aqueous sodium hydroxide (50 c.c.; 0·189 N.) was added to 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (1·011 g.) in alcohol (20 c.c.), and after 15 minutes the mixture was back-titrated with hydrochloric acid (12·0 c.c.; 0·249N.) using phenolphthalein (Found : equiv., 156·5. Calc. : equiv., 157). Hydrochloric acid (9·9 c.c.; 0·249N.) was then added to the neutral liquors until carbon dioxide was no longer liberated, the carbon dioxide was removed by suction, and the excess of hydrochloric acid determined by back-titration with sodium hydroxide (2·3 c.c.; 0·189N.). The amount of carbon dioxide liberated by decarboxylation was thus equivalent to 10·7 c.c. of the standard sodium hydroxide, indicating that about 31% of the oxazolid-2 : 4-dione had been hydrolysed to the carbamate, the remaining 69% having given the carbamate. When 2N-sodium hydroxide was used, the former figure was 32·6%.

3-*Alkyl derivatives of* 5 : 5-*dimethyloxazolid*-2 : 4-*diones*.

Derivative.	M. p.	B. p. at (mm.).	n_D^{20}.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
Pr^n	46—47°	—	—	$C_8H_{13}O_3N$	56·0	7·5	56·1	7·7
Pr^i	89—90	—	—	$C_8H_{13}O_3N$	56·1	7·6	,,	,,
Bu^n	—	68—70° (0·6)	1·4455	$C_9H_{15}O_3N$	58·2	8·2	58·4	8·1
Bu^i	—	64—66 (0·7)	1·4446	$C_9H_{15}O_3N$	58·2	8·0	,,	,,
α-Amyl	—	80—81 (0·5)	1·4470	$C_{10}H_{17}O_3N$	60·6	8·3	60·3	8·6
sssAmyl	—	76—77 (0·7)	1·4456	$C_{10}H_{17}O_3N$	60·9	8·6	,,	,,
CH_2:CH·CH_2	—	82 (4)	1·4590	$C_8H_{11}O_3N$	56·7	6·8	56·8	6·5
CH_2:CMe·CH_2	—	85—87·5 (1·8)	1·4611	$C_9H_{13}O_3N$	58·8	7·6	58·9	7·1
C_6H_5·CH_2	60—61	—	—	$C_{13}H_{13}O_3N$	65·9	6·1	65·8	6·0
HO·CH_2·CH_2	—	119 (0·7)	1·4695	$C_7H_{11}O_4N$	48·6	6·6	48·6	6·4
EtO·CH_2·CH_2	—	76 (0·3)	1·4460	$C_9H_{15}O_4N$	54·0	7·8	53·7	7·5
MeS·CH_2·CH_2	39—40	110 (1·6)	—	$C_8H_{13}O_3NS$	47·2	6·5	47·3	6·4
Et_2N·CH_2·CH_2 *	23—24	107 (2·0)	—	$C_{11}H_{20}O_3N_2$	58·5	8·85	57·8	8·8
,, hydrochloride	190	—	—	$C_{11}H_{21}O_3N_2Cl$	50·0	8·1	49·9	8·0
,, methiodide ...	129—130	—	—	$C_{12}H_{23}O_3N_2I$	38·8	6·3	38·9	6·3
Et_2N·CH_2·CH(OH)·CH_3 †	34	141 (1)	—	$C_{13}H_{25}O_4N_2$	55·3	8·8	55·8	8·6
Hydrochloride	145	—	—	$C_{13}H_{25}O_4N_2Cl$	48·9	7·6	48·9	7·9
CH_3·CO·CH_2·CO·O·CH_2·CH_2 ‡	—	155 (0·7)	1·4713	$C_{11}H_{15}O_5N$	52·0	5·7	51·4	5·9

* *Cf.* Spielman (*loc. cit.*, 1948).

† 3-Diethylamino-2-hydroxypropyl chloride was prepared by the method of Price, Leonard, Peel, and Reitsema (*J. Amer. Chem. Soc.*, 1946, **68**, 1807).

‡ 2-Chloroethyl acetoacetate was prepared as described by Jones, Robinson, and Strachan (*J.*, 1946, 87).

The neutral liquors from 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (10 g.) treated as above with sodium hydroxide (2N.) and hydrochloric acid (2N.), after liberation of carbon dioxide, were extracted continuously with ether and yielded *α-hydroxyisobutyroethylamide* as a hygroscopic soapy solid, m. p. 25—28°, which could not be purified further owing to a tendency to lose ethylamine when heated. It gave a 3 : 5-*dinitrobenzoate*, m. p. 154° (Found : C, 48·4; H, 4·9. $C_{12}H_{13}O_7N_3$ requires C, 48·0; H, 4·6%). The aqueous mother-liquors from extraction of the amide, after acidification with hydrochloric acid and ether-extraction, yielded *N-α-hydroxyisobutyryl-N-ethylcarbamic acid* as colourless prisms (from ether), m. p. 122—123° (decomp.) (Found : C, 48·1; H, 7·4. $C_7H_{13}O_4N$ requires C, 48·0; 7·4%). The carbamic acid (0·535 g.) was heated at 130—140° for 15 minutes; the volume of carbon dioxide evolved was 51 c.c. (75%). When the product was heated on the steam-bath in an open flask with a cold finger inserted at the mouth, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione condensed on the cold finger. The residue, on reacting with 3 : 5-dinitrobenzoyl chloride, furnished the 3 : 5-dinitrobenzoate of α-hydroxyisobutyroethylamide.

(b) 3-*Methyl derivatives*. Hydrolysis of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione was examined as for the 3-ethyl derivative, and the results indicated that about 40% of the hydrolysis occurred by fission of the N-C bond to yield the carbonate. α-Hydroxyisobutyromethylamide was readily obtained with m. p. 78—79° (cf. Spielman, *loc. cit.*) and afforded a 3 : 5-*dinitrobenzoate*, m. p. 162° (Found : C, 46·5; H, 4·3. $C_{11}H_{11}O_7N_3$ requires C, 46·3; H, 4·2%). *N*-α-Hydroxyisobutyryl-*N*-methylcarbamic acid melted at 115° (decomp.).

(c) 3-iso*Propyl derivative*. Hydrolysis of 5 : 5-dimethyl-3-*isopropyl*oxazolid-2 : 4-dione proceeded with the liberation of only 0·15 equivalent of carbon dioxide, indicating that hydrolysis of the lactone preponderated to the extent of 85%. *N-α-Hydroxyisobutyryl-N-isopropylcarbamic acid* had m. p. 150—151° (decomp.) (Found : C, 51·1; H, 8·1. $C_8H_{15}O_4N$ requires C, 50·8; H, 8·0%).

Hydrolysis of 2-Thio-5 : 5-dimethyl-3-ethyloxazolid-4-one (see Part III).—Aqueous sodium hydroxide (50 c.c.; 0·2N.) was added to 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one (1 g.) in alcohol (20 c.c.). After 15 minutes, bromine vapour was drawn through the mixture until it was no longer decolorised. The solution was then made acid to Congo-red with dilute hydrochloric acid, and extracted with ether. Partial evaporation of the extract yielded *N*-α-hydroxyisobutyryl-*N*-ethylcarbamic acid, m. p. 122—123°, identical with the compound described above.

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9. *Derivatives of Oxazolid-2 : 4-dione. Part II. O- and N-Alkylation of 5-Substituted Oxazolid-2 : 4-diones.**

By J. S. H. Davies, M. E. H. Fitzgerald, and W. H. Hook.

A number of new *N*-alkyl derivatives of 5-substituted oxazolid-2 : 4-diones has been prepared. In the reaction of the silver salts of oxazolid-2 : 4-dione and its 5-substituted derivatives with alkyl halides, 5-substitution favours *O*-alkylation.

Spielman (*J. Amer. Chem. Soc.*, 1944, **66**, 1244; 1948, **70**, 1021) has reported the preparation of a number of *N*-alkyl derivatives of oxazolid-2 : 4-diones. The formation of *O*-alkyl derivatives of 5 : 5-dimethyloxazolid-2 : 4-dione and an improved method for the *N*-alkylation of 5 : 5-dimethyloxazolid-2 : 4-dione have been reported in Part I (preceding paper). This work has now been extended in part to oxazolid-2 : 4-dione and to the 5-methyl, 5-methyl-5-ethyl, 5-benzyl-5-methyl, 5-phenyl-5-methyl, and 5 : 5-diphenyl derivatives. The *N*-alkyl derivatives described herein and in Part I have been tested for anti-convulsant activity in mice; detailed results will be published elsewhere.

The oxazolid-2 : 4-diones were prepared from the corresponding glycollic esters by the method of Stoughton (*J. Amer. Chem. Soc.*, 1941, **63**, 2376; U.S.PP. 2,349,313, 2,349,785, 2,372,861). The glycollic esters were prepared by known methods, but in some cases esterification was more efficient by the azeotropic procedure described by Clarke and Davis (*Org. Synth.*, Coll. Vol. I, p. 261) for ethyl oxalate. *Ethyl α-hydroxy-β-phenylisobutyrate*, which was prepared by a modification of Stoughton's method, has not previously been described.

N-Alkylation of 5-substituted oxazolid-2 : 4-diones by the action of the alkylating agent on an alcoholic solution of the sodium salt of the dione, as reported earlier, proceeded normally, but with oxazolid-2 : 4-dione, itself, the yields were in some cases low, probably owing to the high solubility of the products in water.

It was shown (Part I) that reaction of the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione with ethyl iodide in ether at room temperature caused mainly *O*-ethylation with about 10% of *N*-ethylation, but that in boiling toluene up to 30% of the *N*-ethyl derivative was obtained. The silver salt of oxazolid-2 : 4-dione itself, with methyl iodide, gave only the *N*-methyl derivative, 3-methyloxazolid-2 : 4-dione, although the presence of a small proportion of

* Patents pending.

O-methylation product was indicated by the formation of a trace of high-melting product, believed to be 4-imino-oxazol-2-one, when the reaction product was treated with ammonia.

In contrast, the silver salt of 5-benzyl-5-methyloxazolid-2 : 4-dione with ethyl iodide in ether at room temperature readily afforded *4-ethoxy-5-benzyl-5-methyloxazol-2-one*, and the silver salt of 5 : 5-diphenyloxazolid-2 : 4-dione with ethyl iodide in boiling benzene readily gave *4-ethoxy-5 : 5-diphenyloxazol-2-one*; a search for 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione revealed only traces. The amount of *O*- relative to *N*-alkylation in this reaction thus varies with substitution in the 5-position in the order diphenyl- > dimethyl- > unsubstituted oxazolid-2 : 4-dione.

The above-mentioned oxazolones have been isomerised to the corresponding 3-ethyloxazolid-2 : 4-diones by treatment at 180° with ethyl iodide as described in Part I.

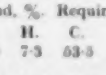
Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s and b. p.s are uncorrected.)

Ethyl α-Hydroxy-β-phenylisobutyrate.—A mixture of benzyl methyl ketone (300 g.) and piperidine (2·5 c.c.) was added slowly during 15 minutes to anhydrous hydrogen cyanide (150 g.), with stirring and cooling. The temperature was allowed to rise to a maximum of 30° and, after completion of addition of the ketone, was reduced to 0°, and stirring was continued for 1 hour. The mixture was then added dropwise to fuming hydrochloric acid (600 c.c.) at 0°, saturated with gaseous hydrogen chloride, stirred at 0° for 4 hours, and allowed to attain room temperature overnight. It was then filtered from precipitated solid and neutralised with aqueous sodium hydroxide (40%), the temperature being maintained below 15°. The precipitate was filtered off and dried. Crystallisation from benzene furnished *α-hydroxy-β-phenylisobutyramide* (211 g.), m. p. 83° (Found: C, 67·2; H, 7·0. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%). The acid was obtained by boiling the amide with sodium hydroxide solution (40%) for 1½ hours and was esterified by the azeotropic method of Clarke and Davis (*loc. cit.*). *Ethyl α-hydroxy-β-phenylisobutyrate* was obtained as a colourless mobile oil, b. p. 141—142°/19 mm., in 65% yield (Found: C, 69·3; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

3-Alkyloxazolid-2 : 4-diones.—The products recorded in the table were prepared as described in Part I by condensing the appropriate α-hydroxy-esters with urea in presence of sodium ethoxide and alkylating the sodium salt of the dione so obtained. They crystallised from methanol, ethanol, or ether.

Preparation of 3-alkyloxazolid-2 : 4-diones.



							Found, %		Required, %		Yield,
R_1.	R_2.	R_3.	M. p.	B. p.	n_D^{20}.	Formula.	C.	H.	C.	H.	%.
H	H	Bu^n	—	137—139°/ 16 mm.	1·4614	$C_7H_{11}O_3N$	53·9	7·3	53·5	7·1	66
H	H	*n*-Amyl	—	144—148/ 15 mm.	1·4605	$C_8H_{13}O_3N$	56·8	8·0	56·2	7·7	51
H	H	CH_2·CH:CH_2	—	72/5 mm.	1·4815	$C_6H_7O_3N$	51·2	5·3	51·1	5·0	23
H	H	CH_2·CMe:CH_2	44—45°	143/13 mm.	—	$C_7H_9O_3N$	54·4	5·9	54·2	5·85	67
H	H	CH_2·C_6H_5	44—45	—	—	$C_{10}H_9O_3N$	62·9	4·8	62·8	4·8	41
H	Me	$[CH_2]_2$·CH_3	—	73—75/ 1 mm.	1·4531	$C_7H_{11}O_3N$	53·2	6·8	53·5	7·1	43
H	Me	$[CH_2]_3$·CH_3	—	84—87/ 1 mm.	1·4530	$C_8H_{13}O_3N$	55·8	7·3	56·1	7·7	54
H	Me	$[CH_2]_4$·CH_3	—	100/ 1·8 mm.	1·4545	$C_9H_{15}O_3N$	58·7	8·1	58·4	8·2	40
H	Me	CH_2·CMe:CH_2	—	128/ 11 mm.	1·4709	$C_8H_{11}O_3N$	57·1	6·7	56·8	6·6	62
H*	Me	CH_2·$COMe$	51—52	139—141/ 2·5 mm.	—	$C_7H_9O_4N$	49·2	5·3	49·1	5·3	70
Me	Et	Et	—	77/2·5 mm.	1·4447	$C_8H_{13}O_3N$	56·1	7·7	56·1	7·7	60
Me	Et	Bu^n	—	90—91/ 3 mm.	1·4459	$C_9H_{15}O_3N$	58·4	8·3	58·4	8·2	59
Me	Et	CH_2·CH:CH_2	—	87·5/ 1·9 mm.	1·4593	$C_9H_{13}O_3N$	58·6	7·1	58·9	7·1	62
Me	CH_2Ph	Et	71—72	—	—	$C_{13}H_{15}O_3N$	67·4	6·7	67·0	6·4	70
Me	Ph	Me	—	168—169/ 18 mm.	—	$C_{11}H_{11}O_3N$	64·0	5·5	64·4	5·4	73
Ph	Ph	Et	90	—	—	$C_{17}H_{15}O_3N$	72·8	5·1	72·6	5·3	55

* *Semicarbazone*, m. p. 193—194°, from ethanol (Found: C, 42·6; H, 5·4. $C_9H_{12}O_4N_4$ requires C, 42·1; H, 5·3%).

Reaction of the Silver Salt of Oxazolid-2 : 4-dione with Methyl Iodide.—The dry silver salt of oxazolid-2 : 4-dione (10 g.), suspended in a mixture of dry ether and methyl iodide (20 c.c.), was set aside at room temperature for 3 days. Filtration, evaporation, and crystallisation of the residue from ether

yielded 3-methyloxazolid-2 : 4-dione (0·75 g.), m. p. and mixed m. p. with an authentic specimen, 134°. Extraction of the filter cake with dry ethanol yielded a further quantity of the 3-methyl derivative. Treatment of the mother-liquors from these extractions with aqueous ammonia, and partial evaporation of the solvents, yielded a product (0·05 g.), presumably *4-imino-oxazol-2-one*, m. p. 215—220° (Found: C, 36·7; H, 3·9. $C_3H_4O_2N_2$ requires C, 36·0; H, 4·0%).

4-Ethoxy-5-benzyl-5-methyloxazol-2-one.—The dry silver salt of 5-benzyl-5-methyloxazolid-2 : 4-dione (11 g.) was suspended in a mixture of dry ether (100 c.c.) and ethyl iodide (20 c.c.), the mixture set aside for 3 days and the solid filtered off. The ether, on distillation, gave a residue (6·0 g.), which on crystallisation from ethanol yielded the *oxazolone* as colourless needles, m. p. 110—111° (Found: C, 67·3; H, 6·6. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·4%).

The oxazolone (1·0 g.) in ethyl iodide (5 c.c.) was heated in a sealed tube at 180° for 20 hours. The product was dissolved in ether, the ethereal solution washed with thiosulphate solution and with sodium carbonate solution, and the solvent distilled. The residue after crystallisation from ether gave 5-benzyl-5-methyl-3-ethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 71—72°.

4-Ethoxy-5 : 5-diphenyloxazol-2-one.—The dry silver salt (18 g.) of 5 : 5-diphenyloxazolid-2 : 4-dione was suspended in a mixture of dry benzene (150 c.c.) and ethyl iodide (15 c.c.). The mixture was boiled under reflux for 2 hours and then filtered and the solvent distilled off from the filtrate. The residue after 3 crystallisations from ether yielded *4-ethoxy-5 : 5-diphenyloxazol-2-one* as colourless prisms, m. p. 100—101° (Found: C, 72·5; H, 5·5. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3%). The total ethereal mother-liquors were shaken for ½ hour with warm dilute hydrochloric acid and then extracted with aqueous sodium hydrogen carbonate to remove 5 : 5-diphenyloxazolid-2 : 4-dione arising from the hydrolysis of any residual oxazolone. The ethereal solution was dried and the solvent distilled, leaving a residue (0·1 g.) from which by crystallisation from ether 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione, identical with an authentic specimen, was obtained.

The oxazolone (0·5 g.) in ethyl iodide (2 c.c.) was heated in a sealed tube at 180° for 20 hours. The product was dissolved in ether, the solution washed with aqueous sodium thiosulphate, and the solvent distilled off. Crystallisation of the residue from ether yielded 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 89—90°.

Our thanks are due to Mr. T. Deegan for some of the preparations, and to Miss Audrey Hudson for pharmacological tests.

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10. *Derivatives of Oxazolid-2 : 4-dione. Part III. The Alkylation of 2-Thio-oxazolid-4-ones.**

By J. S. H. Davies, W. H. Hook, and F. Long.

Alkylation of 2-thio-oxazolid-4-ones yields a mixture of the corresponding 2-thio-3-alkyl-oxazolid-4-ones and 2-alkylthio-oxazol-4-ones. The factors which influence the proportions of *N*- and *S*-alkylation are indicated. A number of 3-alkyloxazolid-2 : 4-diones has been prepared from the 2-thio-3-alkyloxazolid-4-ones.

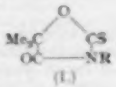
In Parts I and II (preceding papers) the alkylation of the sodium and silver salts of oxazolid-2 : 4-diones has been examined and the results show that the sodium salts are alkylated in the 3-position, *i.e.*, on the *N*-atom, whilst the silver salts give a mixture of the 3-alkyl derivatives and 4-alkoxyoxazol-2-ones, the proportions depending on the temperature (lower temperatures favouring the formation of the latter) and the nature of the substituents in the 5-position. It was also shown that the 4-alkoxyoxazol-2-ones were isomerised by heat to the corresponding 3-alkyloxazolid-2 : 4-diones.

It became of interest, therefore, to examine the alkylation of 2-thio-oxazolid-4-ones, where the effect of tautomerism involving the 2- and 3-positions would be expected to be more pronounced than that of the 3- and 4-positions in oxazolid-2 : 4-diones. A second reason was the fact that 2-thio-3-alkyloxazolid-4-ones, like 2-thio-oxazolid-4-ones themselves, are readily converted into the corresponding oxazolid-2 : 4-diones by a variety of reagents, and the method affords another route to 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, which has been shown to be of value in the treatment of "petit mal" (Lennox, *J. Amer. Med. Assoc.*, 1945, **129**, 1069).

Urech (*Ber.*, 1873, **6**, 1113; 1878, **11**, 467) has shown that 2-thio-5 : 5-dimethyloxazolid-4-one (I; R = H) is formed when an aqueous solution of potassium thiocyanate, potassium cyanide, and acetone is treated with hydrochloric acid. Erlenmeyer, Kleiber, and Loebenstein (*Helv. Chim. Acta*, 1938, **21**, 1010) have similarly prepared 2-thio-5-methyl-5-ethyloxazolid-4-one from methyl ethyl ketone and converted it into 5-methyl-5-ethyloxazolid-2 : 4-dione.

* Patents pending.

Improved conditions for the preparation of these two thio-oxazolidones by Urech's method have been developed and the method has been extended to the preparation of 2-thio-oxazolid-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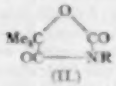
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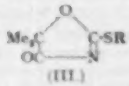
(III.)

4-one from formaldehyde,[1] and of *2-thio-5-methyloxazolid-4-one* from acetaldehyde. The method was most successful for the 5 : 5-dimethyl derivative, which is now readily obtained in 65—75% yield, although the reaction even in this case is very slow. The condensation with methyl ethyl ketone proceeds still more slowly, even on warming, partly owing to the lower solubility of the intermediate cyanohydrin, and the yield of product is much less; and attempts to condense benzyl methyl ketone and acetophenone with cyanide and thiocyanate under these conditions failed.

The alkylation of 2-thio-5 : 5-dimethyloxazolid-4-one has been examined in alcohol, in other organic solvents, such as acetone and benzene, and in water in the presence and absence of various alkaline reagents. The best conditions for 3-alkylation have been applied to the preparation of various 2-thio-3-alkyloxazolid-4-ones and these compounds have been converted into the corresponding oxazolid-2 : 4-diones.

Ethylation of 2-thio-5 : 5-dimethyloxazolid-4-one with ethyl sulphate in ethanol in presence of one equivalent of sodium ethoxide gave an *N*-ethylation product, *2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one* (I; R = Et), and an *S*-ethylation product, *2-ethylthio-5 : 5-dimethyloxazol-4-one* (III; R = Et), which were separated by fractional distillation and crystallisation. The *N*-ethyl derivative is moderately stable to dilute mineral acid, but is hydrolysed by cold aqueous sodium hydroxide to *sodium N-α-hydroxyisobutyryl-N-ethylthiocarbamate* (cf. Part I). It can be determined by titration, as in the case of the 3-alkyloxazolid-2 : 4-diones (Spielman, *J. Amer. Chem. Soc.*, 1944, **66**, 1244), but the end-point is transient owing to the rapid cyclisation of the free thiocarbamic acid to re-form the thio-oxazolidone. 2-Ethylthio-5 : 5-dimethyloxazol-4-one is unstable in moist air and is rapidly hydrolysed by dilute mineral acids to 5 : 5-dimethyloxazolid-2 : 4-dione with evolution of ethanethiol; with aqueous alkali, the hydrolysis proceeds more slowly to form the alkali-metal salt of the oxazolid-dione, but with ammonia 2-imino-5 : 5-dimethyloxazolid-4-one is formed, which is identical with the product prepared by the method of Traube and Ascher (*Ber.*, 1913, **46**, 2077). Preliminary attempts to isomerise the *S*-ethyl to the *N*-ethyl compound were unsuccessful. Methylation of 2-thio-5 : 5-dimethyloxazolid-4-one also gave a mixture; the *S*-methyl derivative was not isolated, but its presence was shown by the evolution of methanethiol on acidification with dilute mineral acid and by the isolation of 5 : 5-dimethyloxazolid-2 : 4-dione from the hydrolysed product.

The ease of hydrolysis of the *S*-methyl derivative afforded a convenient method for the quantitative isolation of the *N*-methyl derivative. The total methylation product was treated with dilute hydrochloric acid, and the oxazolid-dione was separated from the *N*-methyl derivative by extraction with aqueous sodium hydrogen carbonate. This method has been applied throughout for determining the relative amounts of *S*- and *N*-alkylation products formed, the amount of *S*-alkylation being based on the weight of the recovered oxazolid-2 : 4-dione. In ethanol with methyl sulphate and sodium ethoxide, the yield of the 3-methyl derivative was 21% and with potassium ethoxide 27%, but in the absence of an alkaline reagent only *S*-methylation occurred.

In other non-aqueous solvents, such as acetone and benzene, 2-thio-5 : 5-dimethyl-oxazolid-4-one was methylated with methyl sulphate in presence of sodium, potassium, and barium carbonates, the yields in acetone being 31%, 44%, and 49%, respectively, and 20% with potassium carbonate in benzene; with no alkaline reagent present, only partial *S*-methylation took place. It is of interest that when ethylation is carried out in hot commercial dioxan with potassium carbonate and excess of ethyl sulphate the main reaction product is 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. Presumably, the *S*-methyl derivative initially formed is decomposed by potassium carbonate in boiling dioxan, and the resulting oxazolid-dione is then re-alkylated. *2-Thio-3 : 5-dimethyloxazolid-4-one*, *2-thio-3 : 5-dimethyl-5-ethyloxazolid-4-one* and *2-thio-5-methyl-3 : 5-diethyloxazolid-4-one* were prepared by the acetone–potassium carbonate procedure. Benzylation of 2-thio-5 : 5-dimethyloxazolid-4-one in acetone with benzyl bromide and potassium carbonate for 1½ hours gave a small yield of the

3-*benzyl* derivative, which was isolated only with difficulty owing to the presence of considerable quantities of toluene-α-thiol and higher-boiling, related products. The indications were, however, that *S*-benzylation largely predominated. With benzyl chloride for 14 hours, a low yield of 5 : 5-dimethyl-3-benzyloxazolid-2 : 4-dione was obtained.

When methylating 2-thio-5 : 5-dimethyloxazolid-4-one in aqueous solution, it was again found that the proportion of *N*-methylation varied with the nature of the alkaline reagent; with one molecular proportion of potassium hydroxide, the yield of the *N*-methyl derivative was 18% and of *S*-methyl derivative 64% (estimated as the oxazolid-2 : 4-dione); with three molecular proportions of potassium carbonate, the yield of the *N*-methyl derivative rose to 31% with a corresponding decrease in *S*-methylation, but with sodium carbonate or potassium hydrogen carbonate, the yield of the *N*-methyl compound was only about 20%. It will be seen from the foregoing and from the experimental section that the course of methylation is influenced by a number of factors. In aqueous solution, increased alkalinity of the reagent, *e.g.*, the use of potassium carbonate in place of hydrogen carbonate, and increase in size of the cation, *e.g.*, the use of potassium carbonate instead of sodium carbonate, favour *N*-methylation. In alcohol or acetone, the effect of the basic cation is still apparent, the highest yield (49%) of *N*-methylation product being obtained by methylating the barium salt of 2-thion-5 : 5-dimethyloxazolid-4-one in acetone. When considering the effect of solvent alone, it will be seen that the proportion of *N*-methylation increased in the order: benzene < water < alcohol < acetone.

The 2-thio-3-alkyloxazolid-4-ones were readily converted into the corresponding oxazolid-diones by treatment with chlorine or bromine water and also by acid permanganate.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s and b. p.s are uncorrected.)

2-Thio-oxazolid-4-one.—Sodium cyanide (270 g., 5·5 mols.) and potassium thiocyanate (485 g., 5 mols.) were dissolved in water (550 c.c.) and formaldehyde solution (400 c.c., 5 mols.; 37%) was added with cooling and stirring. Concentrated hydrochloric acid (1,250 c.c.) was then added dropwise and the temperature kept below 10°. After filtration from the inorganic salts, the filtrate was set aside for 4 weeks and then continuously extracted with ether. The crude residue (211 g.), obtained after distilling off the ether, was crystallised from water and gave pure 2-thio-oxazolid-4-one (184 g.; 32%), m. p. 113—116° (Found: C, 30·85; H, 2·45; N, 12·4; S, 27·6. Calc. for $C_3H_3O_2NS$: C, 30·8; H, 2·6; N, 11·95; S, 27·4%). Ahlqvist (*J. pr. Chem.*, 1919, [ii], **99**, 56) gives m. p. 111—112°. The yield was raised to 40% by addition of concentrated sulphuric acid to the main filtrate (10% of the volume) and storage for 9 weeks.

By passing bromine vapour into its solution in aqueous methanol, the thio-oxazolidone gave oxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 89—91°.

2-Thio-5-methyloxazolid-4-one.—Sodium cyanide (54 g., 1·1 mols.) and potassium thiocyanate (97 g., 1 mol.) were dissolved in water (125 c.c.), and acetaldehyde (54 g., 1·2 mols.) was added slowly with stirring and good cooling, as much heat is evolved. Concentrated hydrochloric acid (250 c.c.) was added to the stirred mixture, the temperature being kept below 10°. The homogeneous solution was stirred for a further hour, and the inorganic salts were filtered off and washed with diluted hydrochloric acid (20 c.c.; 1 : 1 by vol.). After 1 week, the light-brown crystalline solid (32 g.; 25%) was collected, and sulphuric acid (40 c.c.) added to the filtrate, which on storage for a further 5 weeks deposited a second crop of crystals (38 g.; 29%). The united crops were crystallised from benzene, whereupon *2-thio-5-methyloxazolid-4-one* was obtained as rosettes of colourless, prismatic needles, m. p. 93—94° (Found: C, 37·0; H, 3·8. $C_4H_5O_2NS$ requires C, 36·65; H, 3·8%). The yield on a 5-molar scale was 47%.

2-Thio-5 : 5-dimethyloxazolid-4-one.—Sodium cyanide (270 g., 5·5 mols.) and potassium thiocyanate (65 g.) were dissolved in water (750 c.c.), and acetone (500 c.c., *ca.* 7 mols.) was added. The mixture was stirred and cooled to 0°, and concentrated hydrochloric acid (1,250 c.c.) slowly added during about 5 hours, the temperature being kept below 10°. After 1 hour's stirring the inorganic salts were filtered off and washed with dilute hydrochloric acid (125 c.c.; 1 : 1 by vol.). Potassium thiocyanate (420 g., total of 5 mols.) in water (400 c.c.) was then added to the filtrate kept below 5°. The inorganic salts which separated were filtered off and washed with diluted hydrochloric acid, and the filtrate and washings set aside for 7 days. The first crop of material (204 g.) was filtered off and concentrated sulphuric acid (200 c.c.) added to the filtrate. After 6 weeks another crop (323 g.) separated and after 12 weeks a third crop (19 g.). The united crops were dissolved in ether, the solution filtered from insoluble impurity, the solvent removed, and the residual 2-thio-5 : 5-dimethyloxazolid-4-one (531 g., 73%) crystallised in portions from water. The yield from acetone cyanohydrin and potassium thiocyanate after about 8 weeks was 64%.

2-Thio-5-methyl-5-ethyloxazolid-4-one.—The general procedure of the previous experiments was followed with methyl ethyl ketone (265 c.c., 3 mols.), sodium cyanide (135 g., 2·75 mols.), potassium thiocyanate (242·5 g., 2·5 mols.), water (315 c.c.), and concentrated hydrochloric acid (625 c.c.). Stirring was continued for 16 hours before filtering off the inorganic salts, which were washed with a mixture of water (25 c.c.) and concentrated hydrochloric acid (25 c.c.). The united filtrates and washings were stirred at 40—45° for 8 days and then set aside for 2 days. The yellow solid (155 g.) was filtered off, washed with diluted hydrochloric acid and dried at 50°. Concentrated sulphuric acid (100 c.c.) was added to the united filtrates and washings, followed by enough water to dissolve the oil on the surface of the solution; after 6 weeks a further crop (28 g.) was obtained. The united crops were

dissolved in ether, the solution was filtered, and the solvent distilled from the clear filtrate. The residue, a light-yellow solid (140 g.; 35%), on crystallisation from hot water, furnished 2-thio-5-methyl-5-ethyloxazolid-4-one, colourless needles, m. p. 106°, as described by Erlenmeyer, Kleiber, and Loebenstein (*loc. cit.*).

2-Thio-3 : 5-dimethyloxazolid-4-one.—2-Thio-3-methyloxazolid-4-one (63·5 g., 0·5 mol.), acetone (300 c.c.), and potassium carbonate (87 g., 0·63 mol.) were stirred for 2 hours, methyl sulphate (72 g., 0·57 mol.) was added, and the mixture boiled under reflux for 3 hours; after removal of the acetone, water (200 c.c.) and concentrated hydrochloric acid (75 c.c.) were added in turn. Extraction with carbon tetrachloride, washing the extract with aqueous ammonia (2*N*.) and distillation of the dried solution gave a colourless oil, b. p. 134—146°/15 mm., which solidified, and crystallisation from a mixture of ether and light petroleum (b. p. 30—40°; 1 : 1 by vol.) gave *2-thio-3 : 5-dimethyloxazolid-4-one* as prismatic needles (27·5 g.; 38%), m. p. 74—75° (Found : C, 41·9; H, 4·85. $C_5H_7O_2NS$ requires C, 41·4; H, 4·85%). A current of chlorine was passed through a mixture of the thion compound (20 g.) in carbon tetrachloride (30 c.c.) and water (30 c.c.). Ether-extraction and distillation furnished **3** : 5-dimethyloxazolid-2 : 4-dione as an oil (12·65 g.; 71%), b. p. 116—125°/22 mm. (Found : C, 46·95; H, 5·9. Calc. for $C_5H_7O_3N$: C, 46·5; H, 5·45%).

2-Thio-3 : 5-dimethyl-5-ethyloxazolid-4-one.—2-Thio-5-methyl-5-ethyloxazolid-4-one (31·8 g., 0·2 mol.) in acetone (120 c.c.) was stirred with anhydrous potassium carbonate (34 g., 0·25 mol.) for 2 hours until neutral. Methyl sulphate (28 g., 0·22 mol.) was added dropwise during ½ hour; heat was evolved and the mixture was boiled under reflux for 1½ hours. After removal of the solvent, the residue was stirred with water (80 c.c.), concentrated hydrochloric acid (75 c.c.) was then added and the methanethiol evolved burned in a current of coal gas. Extraction of organic material with carbon tetrachloride, removal of 5-methyl-5-ethyloxazolid-2 : 4-dione with dilute ammonia (100 c.c. ; 2*N*.), drying (Na_2SO_4), and fractional distillation furnished *2-thio-3 : 5-dimethyl-5-ethyloxazolid-4-one* (15·95 g.; 46%) as a colourless oil, b. p. 116—122°/14 mm., which solidified when kept and then melted at 30—33°. Crystallisation from light petroleum (b. p. 40—60°) yielded colourless, prismatic needles, m. p. 34° (Found : C, 48·75; H, 6·3; N, 8·6. $C_7H_{11}O_2NS$ requires C, 48·55; H, 6·35; N, 8·1%). A current of chlorine was passed into a solution of the thion compound (13·15 g.) in carbon tetrachloride (15 c.c.) and water (15 c.c.) for 1½ hours, the temperature being kept below 5°. After neutralisation and extraction with ether, removal of solvents gave an oil (9·9 g.), which on fractionation furnished **3** : 5-dimethyl-5-ethyloxazolid-2 : 4-dione (8 g.; 67%) as a colourless oil, b. p. 100—105°/16 mm. (Found : C, 53·7; H, 7·35; N, 8·25. Calc. for $C_7H_{11}O_3N$: C, 53·5; H, 7·05; N, 8·9%).

2-Thio-5-methyl-3 : 5-diethyloxazolid-4-one.—On replacement of the methyl sulphate by ethyl sulphate (32·4 g., 0·21 mol.) in the above experiment, addition of more acetone (total 250 c.c.), and boiling under reflux for 5 hours, *2-thio-5-methyl-3 : 5-diethyloxazolid-4-one* was obtained first as an oil, b. p. 129—132°/35 mm., which solidified when kept and melted at 29—32°. Crystallisation from light petroleum (b. p. 40—60°) yielded large, colourless prisms (15·4 g.; 41%), m. p. 32—33° (Found : C, 51·4; H, 6·75; N, 8·1. $C_8H_{13}O_2NS$ requires C, 51·35; H, 6·95; N, 7·5%). On hydrolytic de-sulphurisation, the thion compound (12·7 g.) gave 5-methyl-3 : 5-diethyloxazolid-2 : 4-dione as a slightly yellow oil (8·85 g.), b. p. 100—102°/15 mm. (Found : N, 7·9. Calc. for $C_8H_{13}O_3N$: N, 8·2%).

2-Thio-5 : 5-dimethyl-3-ethyloxazolid-4-one and 2-Ethylthio-5 : 5-dimethyloxazol-4-one.—(*a*) 2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) was dissolved in a solution of sodium ethoxide obtained from sodium (4·6 g., 0·2 mol.) and dry ethanol (100 c.c.), and ethyl sulphate (30·8 g., 0·2 mol.) was added to the clear solution. After 6 hours' boiling under reflux, the solution was fractionally distilled in a vacuum. The fraction, b. p. 80—85°/1·5 mm., was crystallised from methanol, giving *2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one* as colourless, glistening plates, m. p. 62—63° (Found : C, 48·9; H, 6·7; S, 18·9. $C_7H_{11}O_2NS$ requires C, 48·6; H, 6·4; S, 18·5%). The fraction, b. p. 85—90°/1·5 mm., crystallised from dry ether to give *2-ethylthio-5 : 5-dimethyloxazol-4-one* as colourless, vitreous prisms, m. p. 27—28° (Found : C, 48·8; H, 6·6; S, 18·5%). When shaken with dilute hydrochloric acid, the oxazolone decomposed evolving ethanethiol and ether-extraction of the liquors gave 5 : 5-dimethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 76—77°. When shaken with aqueous amonia (2*N*.), the oxazolone deposited 2-imino-5 : 5-dimethyloxazolid-4-one, m. p. and mixed m. p. with an authentic specimen, 245—246°. The thio-oxazolidone (17·3 g., 0·1 mol.) in carbon tetrachloride (15 c.c.) was stirred with water (15 c.c.), and chlorine passed through for ½ hour at below 10°. Excess of chlorine was removed by a current of air, the two layers were separated, and the aqueous layer was further extracted with carbon tetrachloride. The united extracts were then washed in turn with aqueous potassium hydrogen carbonate and sodium thiosulphate and then dried, and the solvent distilled off. The residue, on crystallisation from ether, afforded 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, in 90% yield, having m. p. and mixed m. p. with an authentic specimen, 76—77°.

(*b*) 2-Thio-5 : 5-dimethyloxazolid-4-one (145 g., 1 mol.) was dissolved in acetone (1,200 c.c.); after the mixture had been stirred with anhydrous potassium carbonate (170 g., 1·2 mols.) until neutral (3 hours), ethyl sulphate (162 g., 1·05 mols.) was added slowly with vigorous stirring. The mixture soon solidified and it was necessary to break up the mass with a glass rod. The mixture was then boiled under reflux for 1 hour. The acetone was distilled off, finally under reduced pressure, water added, and the mixture stirred to hydrolyse unchanged ethyl sulphate. The mixture was acidified with concentrated hydrochloric acid (150 c.c.), and the ethanethiol evolved burned in a current of coal gas. The solution was extracted with carbon tetrachloride, and the organic layer washed with aqueous potassium carbonate and dried. The crude product after evaporation of the solvent was washed with light petroleum (b. p. 40—60°) and crystallised twice from the same solvent. The yield of 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one thus obtained was 70 g. (40%). The potassium carbonate washings were acidified and 5 : 5-dimethyloxazolid-2 : 4-dione was isolated with the aid of ether.

When the ethylation was carried out in commercial dioxan by the following procedure, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione was obtained. 2-Thio-5 : 5-dimethyloxazolid-4-one (72·5 g., 0·5 mol.) was dissolved in dioxan (300 c.c.), and ethyl sulphate (78 g., 0·51 mol.) was added with stirring. The mixture was boiled under reflux for 4½ hours at a bath temperature of 115°. Anhydrous potassium

carbonate (166 g., 1·2 mols.) was added to the cooled solution, and the mixture warmed slowly to the b. p. under reflux, whereupon ethanethiol was evolved. Ethyl sulphate (78 g., 0·51 mol.) was then added dropwise at the b. p. during 1 hour, and boiling continued for 5 hours. The solvent was then distilled, finally under reduced pressure, and water (200 c.c.) and carbon tetrachloride (50 c.c.) were added. After the mixture had been stirred overnight, concentrated hydrochloric acid (150 c.c.) was added, and a further addition of water (350 c.c.) was necessary to dissolve inorganic salts. The organic layer was separated and the aqueous layer extracted 3 times with carbon tetrachloride. The combined extracts were washed with aqueous ammonia (2N.) and dried (Na_2SO_4). Evaporation yielded a brown oil which partly crystallised and gave 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (41·1 g.; 52%) having m. p. and mixed m. p. with an authentic specimen, 76—77°.

When the ethylation was carried out by heating equimolecular quantities of the thio-oxazolidone and ethyl sulphate for ½ hour at 100—110° (bath temperature), little reaction taking place at 80°; 60% of 5 : 5-dimethyloxazolid-2 : 4-dione and about 5% of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione were isolated after acidification with hydrochloric acid.

2-Thio-3 : 5 : 5-trimethyloxazolid-4-one.—2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) was dissolved in a solution of sodium ethoxide obtained from sodium (4·6 g., 0·2 mol.) and dry ethanol (100 c.c.), and treated dropwise with methyl sulphate (25·2 g., 0·2 mol.). The mixture was boiled under reflux for 1 hour, the alcohol distilled, and the residue stirred with a slight excess of dilute hydrochloric acid; methanethiol was evolved. The product was extracted with ether, the solution washed with aqueous sodium hydrogen carbonate, the solvent distilled, and the residue fractionated. The fraction, b. p. 100—105°/8 mm., was crystallised from aqueous methanol and gave *2-thio-3 : 5 : 5-trimethyloxazolid-4-one* (21%) as colourless, glistening plates, m. p. 54—55° (Found: C, 45·9; H, 5·9; S, 19·6. $C_6H_9O_2NS$ requires C, 45·3; H, 5·7; S, 20·1%). With potassium ethoxide (0·2 mol.) in place of sodium ethoxide, the yield was 27%, and with no alkali present only partial *S*-methylation occurred.

Desulphurisation of the thio-oxazolidone with chlorine or bromine water gave an almost quantitative yield of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 45—46°. Desulphurisation with permanganate was carried out as follows. 2-Thio-3 : 5 : 5-trimethyloxazolid-4-one (31·8 g.) was suspended in water (25 c.c.), and a warm solution of potassium permanganate in sulphuric acid (2N.), saturated at 50°, added in portions with stirring until the solution exhibited a permanent pink colour. The solution was then treated with sulphur dioxide to dissolve oxides of manganese, saturated with salt, and extracted with ether. Evaporation of the dried ethereal solution, followed by cooling to −10°, gave 3 : 5 : 5-trimethyloxazolid-2 : 4-dione in almost quantitative yield.

Methylation of 2-Thio-5 : 5-dimethyloxazolid-4-one in Other Solvents.—(a) *In water.* A solution of the thio-oxazolidone (1 mol.) in an aqueous solution of the alkaline reagent (see below) was cooled in ice, and methyl sulphate (1·3 mols.) was added dropwise with vigorous stirring. Stirring was continued for 24 hours and the solution then made acid to Congo-red with hydrochloric acid. Sufficient carbon tetrachloride to dissolve the precipitated organic solid was added and stirring continued for 2 hours. The solution was then made alkaline with aqueous sodium hydrogen carbonate, and after being stirred for 1 hour the carbon tetrachloride layer was separated, washed with fresh aqueous sodium hydrogen carbonate, dried and distilled. The *N*-methylation product, 2-thio-3 : 5 : 5-trimethyloxazolid-4-one, b. p. 100—105°/8 mm., was collected. 5 : 5-Dimethyloxazolid-2 : 4-dione, formed by decomposition of the *S*-methylation product, was isolated from the acidified mother-liquors and washings by ether-extraction.

The percentages of *N*- and *S*-methylation occurring in aqueous solution with the use of various alkaline reagents are given in the following table.

Alkaline reagent.	*N*-Methylation, %.	*S*-Methylation, %.	Alkaline reagent.	*N*-Methylation, %.	*S*-Methylation, %.
KOH (1 mol.)	18	64	K_2CO_3 (1·5 mols.)	28	60
*KOH (3 mols.)	4	—	K_2CO_3 (3 mols.)	31	56
$KHCO_3$ (3 mols.)	22	60	Na_2CO_3 (3 mols.)	20	65

* The bulk of the product was decomposed by the strong alkali.

(b) *In acetone and benzene.* A solution of the thio-oxazolidone (1 mol.) was stirred with the alkaline reagent (see below) for 2—3 hours to allow the alkali-metal salt to be formed, and methyl sulphate (1·25 mols.) added dropwise to the resulting suspension. The mixture was boiled under reflux for 3 hours, the solvent distilled, and the residue treated with dilute hydrochloric acid and worked up as for methylation in water. In acetone, a lower-boiling by-product, probably *acetone dimethyl mercaptol*, b. p. 56°/17 mm., was obtained (Found: C, 44·1; H, 8·6. $C_5H_{12}S_2$ requires C, 44·1; H, 8·8%).

The amount of *N*-methylation occurring is given in the following table:

Solvent.	Alkaline reagent.	*N*-Methylation, %.	Solvent.	Alkaline reagent.	*N*-Methylation, %.
Acetone	Na_2CO_3 (2 mols.)	31	Benzene ...	K_2CO_3 (2 mols.)	20
	K_2CO_3 (2 mols.)	44		None.	Partial *S*-methylation, only.
	$Ba(OH)_2$–$BaCO_3$	49			

In the experiment with barium hydroxide and barium carbonate, the solution of the thio-oxazolidone was first stirred with an excess of barium hydroxide and then filtered, and methyl sulphate was added to the filtrate in presence of excess of barium carbonate.

2-Thio-3-benzyl-5 : 5-dimethyloxazolid-4-one.—A mixture of 2-thio-5 : 5-dimethyloxazolid-4-one (48 g., 0·33 mol.) in acetone (200 c.c.) and anhydrous potassium carbonate (60 g., 0·43 mol.) was stirred for 2 hours. Benzyl bromide (65 g., 0·38 mol.) was added and the mixture boiled under reflux for 1½ hours. Acetone was distilled off, and the residue stirred with water (150 c.c.) and carbon tetrachloride (200 c.c.). The organic layer was separated, washed with water, and stirred with warm

hydrochloric acid (200 c.c.; 2N.), then washed in turn with water and aqueous ammonia (2N.), dried, and distilled. The fraction, b. p. 174—185°/5 mm., on storage and cooling deposited crystals, m. p. 81—85°. Repeated crystallisation from ether furnished a small quantity of *2-thio-3-benzyl-5 : 5-dimethyloxazolid-4-one*, m. p. 88—89° (Found : C, 61·2; H, 5·8. $C_{12}H_{13}O_2NS$ requires C, 61·25; H, 5·6%).

Under the following conditions of benzylation, 3-benzyl-5 : 5-dimethyloxazolid-2 : 4-dione was the only product obtained pure. 2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) in acetone (120 c.c.) was stirred with anhydrous potassium carbonate (44 g., 0·32 mol.) for 2 hours to form the potassium salt, benzyl chloride (35·5 g., 0·3 mol.) was added, and the mixture was boiled under reflux for 14 hours. After removal of the acetone, water (100 c.c.) and then concentrated hydrochloric acid (100 c.c.) were added, and the mixture was extracted with carbon tetrachloride. The extract was washed with aqueous ammonia (4N.), to remove 5 : 5-dimethyloxazolid-2 : 4-dione, and dried and the solvent distilled. The first fraction, b. p. 94—96°/30 mm., containing toluene-α-thiol and related products, was discarded. The second fraction, a yellow oil, b. p. 164—180°/15 mm., when mixed with ether and light petroleum and cooled gave 3-benzyl-5 : 5-dimethyloxazolid-2 : 4-dione (5·15 g.), which after crystallisation from light petroleum (b. p. 60—80°) had m. p. 56—57° and did not depress the m. p. of an authentic specimen, m. p. 60—61°. Its constitution was confirmed on attempted de-sulphurisation with chlorine water; it was recovered unchanged.

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11. *Potential Trypanocides of the N-Heterocyclic Series. Part II. Analogues of Dimidium Bromide.*

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The synthesis of analogues of dimidium bromide (III; R = Ph), in which the 9-phenyl group is replaced by a *cyclo*hexyl, benzyl, or heteromonocyclic nucleus, has been investigated for correlation of structure with trypanocidal activity. The phenanthridines (II) were readily obtained, but for steric reasons the *cyclo*hexyl compound did not give a quaternary salt. The furyl compound (IIb) decomposed when treated with methyl sulphate, and the pyridylphenanthridine (IIc) yielded a pyridinium salt when treated with methyl iodide or methyl sulphate. The benzyl- and 2-thienyl-phenanthridines (II) were converted into phenanthridinium salts, hydrolysis of which gave respectively highly effective trypanocides of type (III). The dihydropyranylphenanthridine (IId) could be quaternised, but an attempt to hydrolyse the urethane groups of the salt led to decomposition.

2 : 7-Diamino-9-*p*-aminophenyl-10-methylphenanthridinium chloride (III; R = *p*-$NH_2{\cdot}C_6H_4$, A = Cl) and its precursor (III; R = *p*-$NO_2{\cdot}C_6H_4$, A = Cl) are valuable trypanocides, the former being the most active phenanthridinium compound (*T. congolense* and *T. rhodesiense*) investigated to date. The triamino-salt was also obtained by an alternative synthesis.

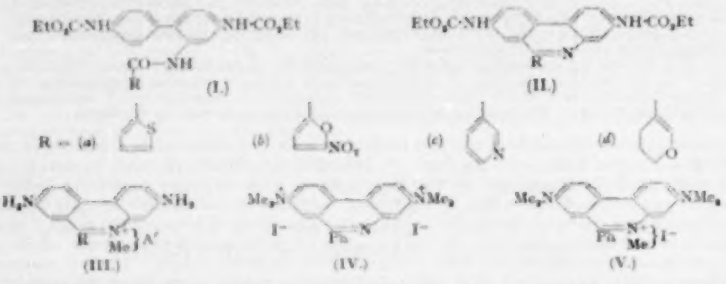
The most active trypanocide of the phenanthridine series yet described is dimidium bromide (III; R = Ph), and it was early suggested (*J.*, 1945, 296) that its activity might be associated in part with the 2 : 7-arrangement of the amino-groups. The molecule contains a benzidine structure and it is well known that derivatives of benzidine are substantive towards vegetable fibres, and that a similar substantivity is frequently a property of trypanocidal drugs. It was desirable to test this hypothesis further by preparing other compounds of the series, which preserve the benzidine structure, but differ in the nature of the 9-substituent. The first compound of this type (III; R = Me) (*J.*, 1947, 68) to be tested is a much less effective trypanocide than dimidium bromide, but this may be the consequence of metabolism rather than of a reduced intrinsic trypanocidal activity. Compounds of the "Sontochin" type, which contain a 3-methylquinoline nucleus, are valuable antimalarials, but analogous compounds with a quinaldine nucleus are inactive and this striking difference is perhaps caused by the presence of the reactive α-methyl group, which may act as a focus for metabolic attack (Walker, *J.*, 1947, 1553). In the phenanthridine series the 9-methyl group is similarly highly reactive.

The 9-*cyclo*hexyl compound differs little from dimidium bromide in fundamental structure and for this reason its synthesis was attempted. *cyclo*Hexanecarboxyl chloride and 2-amino-4 : 4′-biscarbethoxyaminodiphenyl in pyridine furnished a good yield of the *amide* (I; R = C_6H_{11}), which was cyclised by phosphoryl chloride to 2 : 7-*biscarbethoxyamino*-9-cyclo*hexylphenanthridine* (II; R = C_6H_{11}). A quaternary salt could not be obtained from this substance: treatment with nitrobenzene–methyl sulphate at 170° and cooling gave the *sulphate* of the base, but with methyl toluene-*p*-sulphonate no reaction occurred. Even with carefully purified methyl sulphate alone, some sulphate was formed. This experience recalls the similar product obtained from 6-acetamido-2-*p*-aminostyrylquinoline by Browning, Cohen, Cooper, and Gulbransen (*Proc. Roy. Soc.*, B, 1931, **109**, 53), which may very likely have been a sulphate

rather than the postulated complex with methyl sulphate. The failure of the *cyclo*hexyl compound to yield quaternary salts is explicable by steric hindrance: models reveal that the *cyclo*hexyl group offers much more obstruction to accommodation of a methyl group on $N_{(10)}$ than does a phenyl group.

With (III; R = CH_2Ph) an intermediate type between dimidium bromide and (III; R = Me) is under consideration; the methylene group might likewise be regarded as a point of metabolic attack but oxidation of the benzyl compound is less likely to involve the loss of the essential quaternary system. However, 7-amino-9-*p*-aminobenzyl-10-methylphenanthridinium bromide is very much less active than the corresponding *p*-aminophenyl compound (Part I). Condensation of 2-amino-4:4'-biscarbethoxyaminodiphenyl and phenylacetyl chloride afforded *2-phenylacetamido-4:4'-biscarbethoxyaminodiphenyl* (I; R = CH_2Ph) which was smoothly cyclised to *2:7-biscarbethoxyamino-9-benzylphenanthridine* (II; R = CH_2Ph); successive quaternisation and hydrolysis converted this compound into the desired salt (III; R = CH_2Ph, A = Br), which is highly trypanocidal (*Trypanosoma congolense*) although less effective than dimidium bromide.

The effect of replacement of the 9-phenyl group of dimidium bromide by heterocyclic nuclei was also examined, readily accessible nuclei of widely different type being used, namely 2-thienyl, 5-nitro-2-furyl, 3-pyridyl, and 5:6-dihydro-3-pyranyl. 2-Acetylthiophen was oxidised by sodium hypochlorite to thiophen-2-carboxylic acid and the derived chloride was condensed with 2-amino-4:4'-biscarbethoxyaminodiphenyl to yield *2-(thiophene-2''-carboxyamido)-4:4'-biscarbethoxyaminodiphenyl* (Ia). Cyclisation then furnished *2:7-biscarbethoxyamino-9-2'-thienylphenanthridine* (IIa), and this was converted by the customary methods into the quaternary salt (III; R = 2-thienyl, A = Br), which is a more effective trypanocide (*T. congolense*) than dimidium bromide. The 5-nitro-2-furyl nucleus has already been associated with biologically active compounds: furacin (5-nitro-2-furaldeb[illegible] semicarbazone) is an effective antibacterial and as a trypanocide (Dodd and Stillman, *J. Pharm. Exp. Ther.*, 1944, **82**, 11). 5-Nitro-2-furoic acid led, as above, to *2:7-biscarbethoxyamino-9-(5-nitro-2-furyl)phenanthridine* (IIb), but attempts to form quaternary salts caused profound decomposition.



Petrow and Wragg (*J.*, 1947, 1410) have reported that the synthesis of 9-pyridylphenanthridines from 2-nicotinamidodiphenyls may result in low yields, even after prolonged heating with nitrobenzene–phosphoryl chloride. In the initial reaction between the amide and phosphoryl chloride, hydrogen chloride is liberated and thus a proton becomes bound to the pyridine-N. The inductive effect of this positive pole appears to decrease the electrophilic affinity of the amide-C atom and hence retards cyclisation (ring-closure being an electrophilic-substitution reaction). However, in accordance with our experience of *o*-acylamidodiphenyls with urethane substituents, cyclisation of *2-nicotinamido-4:4'-biscarbethoxyaminodiphenyl* (Ic) proceeded under milder conditions, although the yield of the *phenanthridine* (IIc) was rather low (25%). Under similar conditions the *methochloride* of the foregoing amide was recovered unchanged, in confirmation of the retarding effect on ring-closure of a positive pole in the acyl group. With methyl sulphate in nitrobenzene at 135°, or preferably with methyl iodide in refluxing dioxan, the pyridylphenanthridine gave a gum from which, by addition of an excess of aqueous naphthalene-β-sulphonic acid, a colourless, *1'-methonaphthalene-β-sulphonate* **10-naphthalene-β-sulphonate** was obtained. This salt, when treated with aqueous sodium acetate, gave a yellow *methonaphthalene-β-sulphonate* and it is certain that this was the pyridinium salt (Petrow and Wragg, *loc. cit.*) and

not the phenanthridinium salt; since attempts at hydrolysis of the urethane groups did not lead to crystalline products, the series was not examined further. To complete the investigation with 9-heterocyclic substituents, 5 : 6-dihydropyran-3-carboxyl chloride (B.P. 570,974) was condensed with 2-amino-4 : 4'-biscarbethoxyaminodiphenyl and the resultant *amide* (Id) cyclised to 2 : 7-*biscarbethoxyamino*-9-(5 : 6-*dihydro*-3-*pyranyl*)*phenanthridine* (IId). Treatment of this compound with methyl sulphate, followed by metathesis with dilute hydrochloric acid, yielded a yellow *methochloride* but it was not possible to convert this into the diamino-quaternary salt since acid hydrolysis also affected the dihydropyran ring (Schniepp and Geller, *J. Amer. Chem. Soc.*, 1946, **68**, 1646).

A new approach to the production of more active trypanocides followed from the following considerations. 9-Phenyl-10-methylphenanthridinium chloride itself exhibits slight trypanocidal activity; with an amino-substituent in the diphenyl portion of the molecule this activity becomes significant, and reaches a high level with two such substituents (as in dimidium bromide), although one of the two amino-groups may then be located in the 9-phenyl group (*J.*, 1945, 297). It was of interest therefore to examine whether a third amino-group would further enhance the therapeutic effect. 2-p-*Nitrobenzamido*-4 : 4'-*biscarbethoxyaminodiphenyl* (I; R = *p*-NO_2·C_6H_4) was cyclised to 2 : 7-*biscarbethoxyamino*-9-p-*nitrophenylphenanthridine* (II; R = *p*-NO_2·C_6H_4) by phosphoryl chloride. This reacted readily in nitrobenzene with methyl sulphate to give the quaternary *methosulphate*, which afforded a good yield of 2 : 7-*diamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride* (III; R = *p*-NO_2·C_6H_4, A = Cl) when hydrolysed with sulphuric acid (*d* 1·66) at 125—130°. If the reaction temperature was increased to 150—155° some loss of the quaternary group occurred concurrently with hydrolysis of the urethane groups. Reduction of (III; R = *p*-NO_2·C_6H_4, A = Cl) with iron powder and water was unsatisfactory, and the method was not applicable to the corresponding *nitro-diacetamido*-salt. During an examination of numerous reducing agents, however, it was found that heating this salt in water with a 30% excess of ferrous hydroxide (prepared from stoicheiometric quantities of ferrous sulphate and barium hydroxide) gave the *amino-diacetamido*-salt almost quantitatively, and from this 2 : 7-*diamino*-9-p-*aminophenyl*-10-*methylphenanthridinium chloride* (III; R = *p*-NH_2·C_6H_4, A = Cl) was readily obtained by dilute hydrochloric acid. Similarly, by reduction with ferrous hydroxide (a method better suited to nitro-quaternary salts in general than is iron powder, a cleaner product being obtained), the salt (III; R = *p*-NO_2·C_6H_4, A = Cl) was converted directly and quantitatively into the *triamino*-salt (III; R = *p*-NH_2·C_6H_4, A = Cl). Both the nitro-diamino- and triamino-salts are highly trypanocidal, the former being at least equal to dimidium bromide in *T. congolense* infections in mice and dogs, and the latter markedly more active and somewhat less (acutely) toxic. The triamino-salt is also highly active in *T. rhodesiense* infections in mice; in this respect it much exceeds any other phenanthridinium compound yet investigated, being as active as pentamidine although more toxic. None of the compounds here described has a prophylactic action against trypanosomes comparable with that of pentamidine. In an alternative route to the triamino-salt, 4 : 4'-*dinitro*-2-p-*nitrobenzamidodiphenyl* was converted into 2 : 7-*dinitro*-9-p-*nitrophenylphenanthridine* which, unlike dinitro-compounds of the same type, did not yield quaternary salts. The corresponding *triamino*-compound, which is devoid of trypanocidal activity, was converted into the *triacetyl* derivative from which a quaternary *methosulphate* was obtained in rather poor yield. This salt was hydrolysed by dilute acid to the triamino-salt (III; R = *p*-NH_2·C_6H_4, A = Cl).

By methods similar to those already described, 4 : 4'-*biscarbethoxyamino*-2-p-*anisoamido*-*diphenyl* (I; R = *p*-MeO·C_6H_4) was converted into 2 : 7-*biscarbethoxyamino*-9-p-*methoxyphenyl*-*phenanthridine* (II; R = *p*-MeO·C_6H_4) and its *methosulphate*, but the product of hydrolysis of the latter, although undoubtedly containing salts of the type (III), could not be obtained crystalline owing, it is believed, to some simultaneous hydrolysis of the methoxyl group.

Modification of dimidium bromide in a different way was effected as follows. Methylation of 2 : 7-diamino-9-phenylphenanthridine (*J.*, 1945, 299) in aqueous methanol by methyl iodide in the presence of sodium carbonate furnished the white bisquaternary *iodide* (IV) in good yield. Pyrolysis of this salt at 180° caused loss of one mole of methyl iodide and formation of 2 : 7-*bisdimethylamino*-9-*phenyl*-10-*methylphenanthridinium iodide* (V). The corresponding *bromide* is a purple salt, bluer in tint than dimidium bromide, possessing the high antibacterial activity *in vitro* characteristic of phenanthridinium salts, but both this and (V) are practically inactive against trypanosomes. This result suggests that hydrogen-bonding, or some other reaction between drug and substrate not possible with a tertiary amine, is associated with the trypanocidal action of dimidium bromide and its analogues.

Experimental.

(All the products were dried to constant weight before analysis.)

2-cyclo*Hexanecarboxyamido*-4 : 4'-*biscarbethoxyaminodiphenyl* (I; R = C_6H_{11}).—*cyclo*Hexanecarboxyl chloride (26 g.) was added to a suspension of 2-amino-4 : 4'-biscarbethoxyaminodiphenyl (52 g.) in dry pyridine (75 ml.), and the mixture heated on the steam-bath for 15 minutes and then poured into water (2 l.). The oil which separated soon solidified and, when crystallised from alcohol, formed colourless needles (63 g.) of the *amide*, m. p. 184—185° (Found: C, 66·1; H, 6·75; N, 9·5. $C_{32}H_{41}O_5N_3$ requires C, 66·2; H, 6·85; N, 9·25%).

2 : 7-*Biscarbethoxyamino*-9-cyclo*hexylphenanthridine* (II; R = C_6H_{11}).—The amide (I; R = C_6H_{11}) (63 g.) and phosphoryl chloride (63 ml.) were heated at 130° (bath) for 45 minutes. At the outset there was vigorous evolution of hydrogen chloride, and after 15 minutes a yellow solid began to crystallise. The reaction mixture was stirred with ice and an excess of ammonia for a time, then boiled for a few minutes, and cooled, and the aqueous liquor decanted from the rock-like solid. On being heated with alcohol containing a few ml. of concentrated ammonia solution, this solid gave place to colourless prisms which, after cooling, were collected and washed with water and alcohol. The product, 2 : 7-*biscarbethoxyamino*-9-cyclo*hexylphenanthridine* (55 g.), had m. p. 233—234°, unchanged on recrystallisation from alcohol–acetone (Found: C, 69·1; H, 6·65; N, 9·55. $C_{32}H_{39}O_4N_3$ requires C, 68·95; H, 6·65; N, 9·65%). This compound (2 g.), dissolved in nitrobenzene (15 ml.), was treated with methyl sulphate (1·2 ml.) at 170° for 10 minutes. On cooling, a yellow crystalline substance slowly separated, which was not the quaternary salt, for it was hydrolysed by 2*N*-sodium acetate to the starting material. It crystallised from methanol in small yellow needles, m. p. 227—228° (decomp.), and proved to be the *hydrogen sulphate* of the original base (Found: C, 55·5; H, 5·65; N, 7·8; S, 5·8. $C_{32}H_{39}O_4N_3.H_2SO_4$ requires C, 56·25; H, 5·8; N, 7·85; S, 6·0%). The same substance was immediately precipitated on addition of sulphuric acid to a hot nitrobenzene solution of the base.

2-*Phenylacetamido*-4 : 4'-*biscarbethoxyaminodiphenyl* (I; R = CH_2Ph).—Phenylacetyl chloride (5·5 g.) was added to a hot suspension of 2-amino-4 : 4'-biscarbethoxyaminodiphenyl (12 g.) in chlorobenzene (130 ml.), and the mixture refluxed gently for 30 minutes. On cooling, the pure *amide* crystallised as colourless needles (15·1 g.), m. p. 204—205°, unchanged by recrystallisation from alcohol (Found: C, 68·2; H, 5·95; N, 9·15. $C_{32}H_{33}O_5N_3$ requires C, 67·65; H, 5·9; N, 9·1%).

2 : 7-*Biscarbethoxyamino*-9-*benzylphenanthridine* (II; R = CH_2Ph).—The amide (I; R = CH_2Ph) (13·2 g.) and phosphoryl chloride (40 ml.) were refluxed for 1 hour, cooled, and poured into water. After cooling, the deep-yellow solid was collected and dissolved in pyridine, and the solution diluted with water; the precipitate formed was washed thoroughly with water, followed by methanol. The *phenanthridine* (11·4 g.) had m. p. 253° (decomp.) raised to 259° (decomp.) by recrystallisation from acetone or aqueous pyridine (Found: C, 70·55; H, 5·45; N, 9·5. $C_{32}H_{31}O_4N_3$ requires C, 70·4; H, 5·7; N, 9·5%).

Methyl sulphate (10 ml.) was added to a solution of this base (10 g.) in nitrobenzene (80 ml.) at 170°, and the temperature maintained at 160—165° for 3 minutes. The yellow solid, which crystallised out rapidly on cooling, was collected, washed with benzene, dried, and extracted with boiling water. Addition of 2*N*-hydrochloric acid to the filtered aqueous solution precipitated the *methochloride* (7·2 g.), m. p. 253° (decomp.), which crystallised from methanol in small bright yellow blades, m. p. 254° (decomp.) (Found: N, 8·35; Cl, 7·15. $C_{33}H_{34}O_4N_3Cl$ requires N, 8·5; Cl, 7·2%).

2 : 7-*Diamino*-9-*benzyl*-10-*methylphenanthridinium Bromide* (III; R = CH_2Ph, A = Br).—The foregoing methochloride (7·9 g.), concentrated sulphuric acid (28 ml.), and water (24 ml.) were heated at 150° until effervescence ceased (*ca.* 30 minutes), and then poured into water, and the red solution was carefully neutralised with aqueous ammonia. The gum which separated readily solidified; it was dissolved in water, and the filtered solution treated with potassium bromide to precipitate 2 : 7-*diamino*-9-*benzyl*-10-*methylphenanthridinium bromide* (5·8 g.) as a hydrate of indefinite m. p. Crystallisation from methanol yielded purple needles, m. p. 250—252° (Found: N, 10·65; Br, 20·1. $C_{21}H_{20}N_3Br$ requires N, 10·65; Br, 30·3%).

Thiophen-2-carboxylic Acid.—2-Acetylthiophen (60 g.) (prepared according to Hartough and Kosak, *J. Amer. Chem. Soc.*, 1947, **69**, 1012) was covered with 10% sodium hypochlorite solution (500 g.) and vigorously stirred on the steam-bath. A vigorous reaction ensued and chloroform was evolved. Heating was then discontinued and, when the reaction had subsided, more hypochlorite solution was added in portions of 50 g. until chloroform was no longer evolved. After cooling of the mixture a slight excess of liquid sulphur dioxide was added, and the solution acidified with sulphuric acid and extracted with ether. The extract was shaken with sodium hydroxide solution, and the aqueous layer separated and aerated until all traces of ether were removed. Acidification with sulphuric acid precipitated thiophen-2-carboxylic acid (45—50 g.), m. p. 124—125°.

2''-(*Thiophen-2-carboxy*)*amido*-4 : 4'-*biscarbethoxyaminodiphenyl* (Ia).—A mixture of 2-amino-4 : 4'-biscarbethoxyaminodiphenyl (70·5 g.), nitrobenzene (300 ml.), and thiophen-2-carboxyl chloride (30 g.) was heated in a bath at 150° for 2 hours, and the solution left overnight. The crystalline product was collected, washed with nitrobenzene, treated with hot alcohol (300 ml.), and heated for a few minutes. On cooling, the pure *amide* separated as dense colourless prisms (79 g.), m. p. 197—198°, unchanged on recrystallisation from "Cellosolve" (Found: N, 9·3; S, 7·3. $C_{29}H_{29}O_5N_3S$ requires N, 9·25; S, 7·05%).

2 : 7-*Biscarbethoxyamino*-9-2'-*thienylphenanthridine* (IIa).—The amide (Ia) (79 g.) and phosphoryl chloride (80 ml.) were heated at 130—135° (bath) for 75 minutes, cooled, poured on ice, and neutralised with aqueous ammonia. The solid product was dissolved in hot pyridine, diluted with water, and cooled, and small quantities of glacial acetic acid were added with stirring until the oil solidified. A solution of this material in hot glacial acetic acid (400 ml.) was treated with concentrated hydrochloric acid (40 ml.) and, after cooling, the red needles were collected and recrystallised from glacial acetic acid. The hydrochloride thus obtained was dissolved in hot alcohol, and neutralised with the minimum quantity of concentrated aqueous ammonia (until the red colour had given place to yellow), and a seed of the product was introduced. Almost immediately the *phenanthridine* separated as pale yellow prisms (35 g.),

m. p. 227—229° (decomp.), raised to 229—230° (decomp.) on recrystallisation from alcohol–acetone (Found : N, 9·75; S 7·4. $C_{28}H_{21}O_4N_5S$ requires N 9·65; S 7·35%).

2 : 7-*Biscarbethoxyamino-9-2′-thienyl-10-methylphenanthridinium Chloride*.—To (IIa) (16 g.) in nitrobenzene (80 ml.) at 120°, methyl sulphate (24 ml.) was added. The mixture was heated to 135° and then cooled immediately. The orange plates (18 g.) that separated were washed with benzene and dissolved in hot water, and concentrated hydrochloric acid was added to precipitate the *methochloride*, which crystallised from water containing a few drops of 2N-hydrochloric acid, in fine orange needles (16 g.), m. p. 239° (decomp.) (Found : N, 8·7; S, 6·95; Cl, 7·4. $C_{24}H_{24}O_4N_4ClS$ requires N, 8·65; S 6·6; Cl, 7·3%).

2 : 7-*Diamino-9-2′-thienyl-10-methylphenanthridinium bromide* (III; R = 2-thienyl, A = Br) was obtained by hydrolysis of the foregoing methochloride (11·5 g.) with aqueous sulphuric acid (*d* 1·53) at 135—140°. From a solution of the crude bromide in hot alcohol a mixture of black needles and a fine crystalline precipitate separated with cooling, of which only the former were soluble in cold water. An aqueous extract was treated with potassium bromide, and the precipitated material crystallised from alcohol in deep-purple prisms and needles of 2 : 7-diamino-9-2′-thienyl-10-methylphenanthridinium bromide (5·6 g.), m. p. 256° (decomp.) (Found : N, 10·9; S, 8·3; Br, 20·5. $C_{18}H_{16}N_4SBr$ requires N, 10·85; S, 8·3; Br, 20·7%).

2-(5-*Nitro-2-furoamido*)-4 : 4′-*biscarbethoxyaminodiphenyl* (Ib).—This *amide* was the product of condensation of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (75 g.) and 5-nitro-2-furoyl chloride (30 g.) in dry pyridine (150 ml.); it crystallised from glacial acetic acid in yellowish-brown prisms (95 g.), m. p. 223—225° (Found : C, 57·0; H, 4·45; N, 11·85. $C_{30}H_{29}O_9N_5$ requires C, 57·25; H, 4·55; N, 11·6%).

2 : 7-*Biscarbethoxyamino-9-(5-nitro-2-furyl)phenanthridine* (IIb).—The amide (Ib) (95 g.) was cyclised with phosphoryl chloride. The crude product was dissolved in hot pyridine, water added, and the precipitated black solid refluxed with glacial acetic acid (500 ml.) and cooled. The brown residue (18 g.), m. p. 275—277° (decomp.), was crystallised from pyridine, the *phenanthridine* separating as red prisms (15·5 g.) containing pyridine of crystallisation (11·5%); at 125° the prisms lost pyridine and became yellowish-brown, melting at 286—288° (decomp.) (Found : C, 59·6; H, 4·5; N, 12·15. $C_{30}H_{29}O_7N_5$ requires C, 59·5; H, 4·3; N, 12·05%).

2-*Nicotinamido*-4 : 4′-*biscarbethoxyaminodiphenyl* (Ic).—2-Amino-4 : 4′-biscarbethoxyaminodiphenyl (27·5 g.) was treated with nicotinyl chloride hydrochloride [prepared from nicotinic acid (10 g.) and thionyl chloride] in dry pyridine (100 ml.). The reaction product gave, on being refluxed in alcohol (1000 ml.) and cooled, colourless prisms of the *amide* (27 g.), m. p. 228—229° (decomp.) unchanged on recrystallisation from "Cellosolve" (Found : C, 64·4; H, 5·45; N, 12·4. $C_{30}H_{30}O_7N_4$ requires C, 64·3; H, 5·35; N, 12·5%). The substance (5 g.) was heated with alcohol (25 ml.) containing methyl iodide (5 ml.) in a pressure bottle at 100° for 40 minutes, and then evaporated to dryness, and the residue extracted with hot water. From the filtered solution fine colourless needles (5·2 g.) of the *methiodide*, m. p. 159—161° (decomp.), of (Ic) separated on cooling; when recrystallised from alcohol the needles had m. p. 162° (decomp.) (Found : N, 9·55; I, 21·35. $C_{31}H_{33}O_7N_4I$ requires N, 9·5; I, 21·55%).

2 : 7-*Biscarbethoxyamino-9-3′-pyridylphenanthridine* (IIc).—(Ic) (46 g.), phosphoryl chloride (46 ml.), and nitrobenzene (46 ml.) were heated at 130° (bath) for 1 hour and then poured on ice, and the nitrobenzene distilled with steam. On neutralisation of the aqueous residue with ammonia solution and cooling, an amorphous product (41 g.) was obtained, which was digested with hot 0·5N-hydrochloric acid (650 ml.) and left overnight. Unchanged amide (10 g.) was separated by centrifugation and washed with 0·5N-hydrochloric acid, and the aqueous liquors were heated with an excess of naphthalene-β-sulphonic acid. On cooling, colourless prisms (25 g.) separated, which were washed with aqueous naphthalene-β-sulphonic acid, suspended in water, and boiled for a few minutes with a slight excess of aqueous ammonia. The precipitate was extracted with cold 0·5N-hydrochloric acid (200 ml.), and the filtered solution neutralised with aqueous ammonia; the product (9 g.) was further purified by chromatography (Al_2O_3) in acetone solution, and crystallised from alcohol. 2 : 7-*Biscarbethoxyamino-9-3′-pyridylphenanthridine* was obtained as almost colourless prisms and needles (7·8 g.), m. p. 196—198° (decomp.) (Found : C, 66·8; H, 5·4; N, 12·9. $C_{34}H_{32}O_4N_4$ requires C, 66·95; H, 5·1; N, 13·0%).

2 : 7-*Biscarbethoxyamino-9-3′-pyridylphenanthridine* 1′-*Methonaphthalene-β-sulphonate*.—(IIc) (10·6 g.), dioxan (50 ml.), and methyl iodide (11 ml.) were refluxed for 1 hour and then cooled, and the gum left after decantation dissolved in hot water (*ca.* 250 ml.) containing a few drops of glacial acetic acid. After cooling, the filtered solution was reheated, and an excess of naphthalene-β-sulphonic acid added to precipitate the 1′-*methonaphthalene-β-sulphonate* 10-*naphthalene-β-sulphonate*, which crystallised from methanol as colourless prisms (9·9 g.), m. p. 228—229° (decomp.) (Found : N, 6·45; S, 7·55. $C_{31}H_{32}O_7N_4S,C_{10}H_7SO_3H$ requires N, 6·5; S, 7·45%). When this substance was boiled with an excess of aqueous sodium acetate, the prisms gave place to yellow needles of the 1′-*methonaphthalene-β-sulphonate* which, after cooling, were collected, and recrystallised from alcohol in yellow prisms, m. p. 142° (decomp.) (Found : N, 8·7; S, 5·15. $C_{31}H_{32}O_7N_4S$ requires N, 8·6; S, 4·9%).

2-(5 : 6-*Dihydropyran-3-carboxyamido*)-4 : 4′-*biscarbethoxyaminodiphenyl* (Id).—This was prepared by reaction of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (24 g.) with 5 : 6-dihydropyran-3-carboxyl chloride (10·8 g.) in dry pyridine (50 ml.). After recrystallisation from alcohol, the *amide* (21·5 g.) had m. p. 186—188° (Found : C, 63·55; H, 5·55; N, 9·4. $C_{34}H_{37}O_8N_3$ requires C, 63·55; H, 5·95; N, 9·25%).

2 : 7-*Biscarbethoxyamino-9-(5 : 6-dihydro-3-pyranyl)phenanthridine* (IId).—Cyclisation of (Id) with phosphoryl chloride at 130° yielded a crude mixture from which the product was isolated as a hydrobromide and then converted into the free base by aqueous ammonia. Recrystallisation from alcohol–acetone afforded a 15% yield of the *phenanthridine* as colourless prisms, m. p. 215—216° (Found : C, 66·2; H, 5·8; N, 10·2. $C_{34}H_{35}O_6N_3$ requires C, 66·2; H, 5·75; N, 9·65%). The substance (3·5 g.) was heated in nitrobenzene with methyl sulphate at 135° for 5 minutes, and then poured into benzene. The precipitated solid gave, by metathesis with dilute hydrochloric acid (*ca.* 0·1N), the *methochloride* (4·1 g.) as yellow needles, m. p. 256—258° (decomp.), raised to 260° (decomp.) on recrystallisation from water (Found : N, 9·0; Cl, 7·45. $C_{35}H_{38}O_6N_3Cl$ requires N, 8·65; Cl, 7·3%).

2 : 7-*Biscarbethoxyamino-9-p-nitrophenylphenanthridine* (II; R = *p*-$NO_2{\cdot}C_6H_4$).—2-Amino-4 : 4′-bis-

carbethoxyaminodiphenyl (69 g.) and *p*-nitrobenzoyl chloride (42 g.) were heated in nitrobenzene (280 ml.) at 150° for 30 minutes and then cooled, and the product that separated recrystallised from alcohol. **2-p-*Nitrobenzamido*-4 : 4'-*biscarbethoxyaminodiphenyl*** (I; R = *p*-$NO_2C_6H_4$) crystallised in yellow prisms (84 g.), m. p. 202° (Found : C, 60·85; H, 4·75; N, 11·45. $C_{31}H_{34}O_7N_4$ requires C, 60·95; H, 4·9; N, 11·4%). This substance (80 g.) was cyclised with phosphoryl chloride, the ***phenanthridine*** (46 g.) crystallising from pyridine in spherical aggregates of fine yellow needles, m. p. *ca.* 247° (decomp.) (Found : C, 63·2; H, 4·4; N, 11·75. $C_{31}H_{30}O_6N_4$ requires C, 63·2; H, 4·65; N, 11·8%).

2 : 7-*Diamino*-9-*p*-*nitrophenyl*-10-*methylphenanthridinium Chloride* (III; R = *p*-$NO_2C_6H_4$, A = Cl). —(II; R = *p*-$NO_2C_6H_4$) (82 g.) was treated with methyl sulphate (70 ml.) in nitrobenzene solution (500 ml.) in the same manner as the corresponding thienyl compound. The orange solid obtained was refluxed with acetone (400 ml.) for a few minutes and then cooled, and the **2 : 7-*biscarbethoxyamino*-9-*p*-*nitrophenyl*-10-*methylphenanthridinium methyl sulphate*** (96 g.) (containing a small quantity of sulphate), m. p. *ca.* 238° (decomp.), collected. Recrystallisation from methanol yielded pure methosulphate as orange needles, m. p. *ca.* 240—241° (decomp.) (Found : C, 54·1; H, 4·45; N, 9·6; S, 3·35. $C_{31}H_{34}O_{10}N_4S$ requires C, 54·0; H, 4·65; N, 9·35; S, 3·35%). Hydrolysis of this substance (96 g.) with aqueous sulphuric acid (*d* 1·66) at 125—130° for 30 minutes, followed by metathesis of the product with sodium chloride, gave **2 : 7-*diamino*-9-*p*-*nitrophenyl*-10-*methylphenanthridinium chloride***, which crystallised from water in dark purple prisms (51·5 g.), m. p. *ca.* 235° (decomp.) (Found : C, 63·3; H, 4·25; N, 14·45; Cl, 9·25. $C_{20}H_{17}O_2N_5Cl$ requires C, 63·05; H, 4·45; N, 14·7; Cl, 9·35%).

2 : 7-*Diacetamido*-9-*p*-*nitrophenyl*-10-*methylphenanthridinium Chloride*.—Acetic anhydride (10 ml.) was added to a hot suspension of (III; R = *p*-$NO_2C_6H_4$; A = Cl) (5 g.) in glacial acetic acid (50 ml.), and the whole heated for 30 minutes on the steam-bath. The cooled product was collected and recrystallised from water as fine orange needles of the ***nitro-diacetamido*-salt** (4·7 g.), m. p. >300° (Found : N, 12·9; Cl, 7·35. $C_{24}H_{21}O_4N_5Cl$ requires N, 12·65; Cl, 7·65%).

2 : 7-*Diacetamido*-9-*p*-*aminophenyl*-10-*methylphenanthridinium Chloride*.—Solutions of ferrous sulphate heptahydrate (33 g.) and barium hydroxide octahydrate (36 g.) in hot water were mixed, and the resultant sludge added to a stirred suspension of the foregoing nitro-diacetamido-salt (7·5 g.) in water (1500 ml.) at 90—95°. After being heated on the steam-bath for 30 minutes, the mixture was filtered through a preheated funnel, and the residue washed with hot water. The aqueous filtrate was again heated to 90—95° and subjected to further interaction with ferrous hydroxide, prepared from ferrous sulphate (16·5 g.) and barium hydroxide (18 g.), for 30 minutes. The hot aqueous filtrate was treated with sodium chloride to precipitate the ***amino-diacetamido*-salt**, which crystallised from water in small yellow needles (6·1 g.), m. p. *ca.* 280—281° (decomp.) (Found : N, 12·8; Cl, 8·2. $C_{24}H_{23}O_2N_5Cl$ requires N, 12·9; Cl, 8·15%).

2 : 7-*Diamino*-9-*p*-*aminophenyl*-10-*methylphenanthridinium Chloride* (III; R = *p*-$NH_2C_6H_4$, A = Cl).—(*a*) The amino-diacetamido-salt (6·05 g.) and 28-hydrochloric acid (60 ml.) were refluxed for 1 hour, and the red solution was diluted with water (140 ml.) and neutralised carefully with aqueous ammonia; the separation of red prisms was completed by addition of sodium chloride. Recrystallisation from water (40 ml.) containing sodium chloride (0·5 g.) yielded dark red pyramids of the ***triamino*-salt** (4·7 g.), m. p. *ca.* 240° (decomp.) (Found : N, 16·0; Cl, 10·1. $C_{20}H_{19}N_5Cl$ requires N, 16·0; Cl, 10·15%).

(*b*) Reduction of (III; R = *p*-$NO_2C_6H_4$, A = Cl) (30·5 g.) with ferrous hydroxide, prepared from ferrous sulphate (224 g.) and barium hydroxide (240 g.), according to the method just described, yielded a red aqueous solution which was concentrated to *ca.* 500 ml. Metathesis with sodium chloride gave red prisms which, on recrystallisation as in (*a*), yielded dark red pyramids of the same triamino-salt (26·2 g.), m. p. *ca.* 240° (decomp.).

(*c*) Equimolecular quantities of **4 : 4'-dinitro-2-aminodiphenyl** and *p*-nitrobenzoyl chloride were condensed in boiling nitrobenzene. After evolution of hydrogen chloride had ceased, the solution was cooled to allow separation of **2-p-*nitrobenzamido*-4 : 4'-*dinitrodiphenyl*** in almost quantitative yield. Recrystallisation from aqueous pyridine furnished small yellow prisms, m. p. 234° (Found : C, 56·2; H, 2·9; N, 13·75. $C_{19}H_{12}O_7N_4$ requires C, 55·85; H, 2·95; N, 13·7%). When this amide was refluxed in nitrobenzene–phosphoryl chloride for several hours (B.P. 520,273) **2 : 7-*dinitro*-9-*p*-*nitrophenylphenanthridine*** crystallised almost quantitatively in cream-coloured needles; recrystallisation from nitrobenzene gave a product, m. p. 356—358° (Found : C, 58·6; H, 2·15; N, 14·35. $C_{19}H_{10}O_6N_4$ requires C, 58·45; H, 2·6; N, 14·35%). The foregoing powdered trinitro-compound (5 g.) was suspended in alcohol (125 ml.), concentrated hydrochloric acid (25 ml.) and crystalline stannous chloride (30 g.) were added, and the mixture was refluxed for 2 hours. After cooling, the dark red solid was collected, dissolved in hot water, separated from unchanged trinitro-compound (1·1 g.), and then stirred into excess of sodium hydroxide solution. **2 : 7-*Diamino*-9-*p*-*aminophenylphenanthridine*** was thus precipitated as a yellow solid, which crystallised from alcohol in yellow plates, m. p. 246° (Found : C, 76·0; H, 5·45; N, 18·35. $C_{19}H_{16}N_4$ requires C, 76·0; H, 5·35; N, 18·65%). This base was extremely soluble in dilute acid, affording intense carmine solutions. It was acetylated by acetic anhydride–acetic acid; on dilution of the solution thus obtained with water an orange gel formed, which was converted into a flocculent precipitate by the addition of aqueous ammonia. Crystallisation of this product from alcohol afforded **2 : 7-*diacetamido*-9-*p*-*acetamidophenylphenanthridine*** in cream-coloured wool-like needles, m. p. 312° (Found : C, 69·9; H, 5·65; N, 13·25. $C_{23}H_{20}O_2N_4$ requires C, 70·4; H, 5·2; N, 13·15%). A suspension of this compound (5 g.) in nitrobenzene (150 ml.) at 180° was treated with methyl sulphate (5 g.). The gum that separated was isolated by decantation and refluxed with alcohol (200 ml.). The **2 : 7 : 4'-*triacetamido*-9-*phenyl*-10-*methylphenanthridinium sulphate*** thus left undissolved crystallised from methanol in orange plates (2 g.), m. p. 248° (decomp.) [Found : C, 63·95; H, 5·35; N, 11·05. $(C_{30}H_{28}O_3N_5)_2SO_4$ requires C, 63·8; H, 5·15; N, 11·45%]. Hydrolysis of this salt could be affected by refluxing it with N-hydrochloric acid until a clear solution was obtained (several days); more conveniently and with less serious bumping the salt (0·4 g.) was heated in suspension in 10% methanolic hydrochloric acid (15 ml.) until all had dissolved (*ca.* 6 hours), the solution being then evaporated to small bulk. When the residue was neutralised with aqueous ammonia the triamino-salt separated and was purified as in (*a*) (Found : N, 15·6; Cl, 10·1%).

2 : 7-*Biscarbethoxyamino-9-p-methoxyphenylphenanthridine* (II; R = *p*-MeO·C_6H_4).—Condensation of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl and *p*-anisoyl chloride in boiling chlorobenzene furnished 2-*p*-*anisamido*-4 : 4′-*biscarbethoxyaminodiphenyl* (I; R = *p*-MeO·C_6H_4); this amide crystallised from benzene in colourless plates of indefinite m. p. 160—165° (Found: N, 8·95. $C_{34}H_{31}O_6N_3$ requires N, 8·9%). Cyclisation with phosphoryl chloride converted it in a high yield into the *phenanthridine*, which crystallised from alcohol in white microscopic needles, m. p. 190—192° (effervescence) (Found: N, 9·05. $C_{34}H_{29}O_4N_3$ requires N, 9·15%). Its quaternary *methosulphate*, m. p. *ca.* 230°, crystallised from water in deep-yellow needles (Found: N, 7·15; S, 5·45. $C_{35}H_{33}O_7N_3S$ requires N, 7·2; S, 5·45%).

9-*Phenylphenanthridine*-2 : 7-*bistrimethylammonium Iodide* (IV).—2 : 7-Diamino-9-phenylphenanthridine (10 g.) and sodium carbonate (18 g., anhydrous) were refluxed with methanol (100 ml.), water (24 ml.), and methyl iodide (30 ml.) for 8 hours. Two layers at first appeared, but eventually mixed to a deep-purple solution from which crystals slowly separated. The crystals were collected, washed with a little methanol and then with water, and recrystallised from either of these solvents in white needles (14 g.). This salt became yellow at 160°, and with further heating blue-grey, melting at 255° (decomp.) (Found: N, 6·95; I, 40·75. $C_{23}H_{28}N_3I_2$ requires N, 6·7; I, 40·65%).

2 : 7-*Bisdimethylamino-9-phenyl*-10-*methylphenanthridinium Iodide* (V).—The foregoing bisquaternary salt (2·5 g.) was heated in a bath at 180°. Evolution of methyl iodide was observed and after 30 minutes the purple-black mass was extracted with boiling benzene. The residue crystallised from methanol in black needles (1·5 g.) (reddish-purple by transmitted light), m. p. 260—262° (decomp.) (Found: N, 8·8; I, 26·1. $C_{24}H_{26}N_3I$ requires N, 8·7; I, 26·3%). The benzene extract contained a small amount of basic substance, which was not further investigated.

We thank Dr. A. G. Caldwell for the preparation of the benzyl compounds, Mr. L. G. Goodwin and his colleagues of the Wellcome Laboratories of Tropical Medicine for the trypanocidal data, and Mr. A. Bennett for the micro-analyses.

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12. *Catalysed Hydrogen Peroxide Oxidation of Aromatic Hydrocarbons. Part I.*

By J. W. COOK and (MISS) R. SCHOENTAL.

A study has been made of the products formed by oxidation of a series of aromatic hydrocarbons (benzene, naphthalene, phenanthrene, anthracene, 1 : 2-benzanthracene, 1 : 2-5 : 6-dibenzanthracene, chrysene, pyrene, and 3 : 4-benzpyrene) with Milas's reagent (hydrogen peroxide in *tert.*-butanol, catalysed by osmium tetroxide). The reagent was diluted with acetone to promote solubility of the polycyclic hydrocarbons, which are sparingly soluble in *tert.*-butanol; the presence of acetone appeared to have no significant influence on the course of the reaction. The products isolated included a *cis*-diol (in the case of phenanthrene and 1 : 2-benzanthracene), quinones, and acids formed by ring-fission.

1 : 2-Benzanthracene and 1 : 2-5 : 6-dibenzanthracene gave not only the 9 : 10-quinones but also the 3 : 4-quinones (XII and XIV) and in spite of the relatively low yields the method furnishes a convenient method of preparation of these *ortho*-quinones. Benzene gave, together with other products, *allo*mucic acid, an interesting example of a simple and direct route from an aromatic hydrocarbon to a sugar acid.

The mechanism of these transformations is discussed, and attention is drawn to their bearing on the mode of biochemical oxidation of the hydrocarbons, for which an exact parallel by purely chemical methods has yet to be found.

THE authors have shown (Cook and Schoental, *J.*, 1948, 170; *Nature*, 1948, **161**, 237) that oxidation of polycyclic aromatic hydrocarbons with Criegee's osmium tetroxide reagent (osmium tetroxide in benzene–pyridine, followed by hydrolysis of the resulting osmic ester) leads to smooth perhydroxylation with formation of homogeneous α-glycols. From the work of Criegee (*Annalen*, 1936, **522**, 75; 1942, **550**, 99) these were clearly *cis*-α-glycols. In nearly every case the positions attacked were different from those at which oxidation is effected by other reagents. The products of osmium tetroxide oxidation were similar in type to some of the compounds which have been isolated from the excreta of animals to which the hydrocarbons were administered (Boyland and Levi, *Biochem. J.*, 1935, **29**, 2679; Boyland and Shoppee, *J.*, 1947, 801; Boyland and Wolf, *Biochem. J.*, 1948, **42**, XXXII; Booth and Boyland, *ibid.*, 1947, **41**, XXIX; 1949, **44**, 361). Such metabolic glycols are probably intermediates in the formation of the phenols which have been isolated in other cases (see, *e.g.*, Weigert and Mottram, *Cancer Res.*, 1946, **6**, 109; Berenblum and Schoental, *ibid.*, p. 699; *Biochem. J.*, 1949, **44**, 604). There are, however, important differences between the osmium tetroxide oxidations and the biochemical oxidations. Usually the positions in the molecules at which oxidation occurs are different in the two cases. Moreover, evidence is accumulating that the metabolic diols which have been isolated are *trans*-α-glycols. The experiments now recorded were initiated in an endeavour to find a reagent

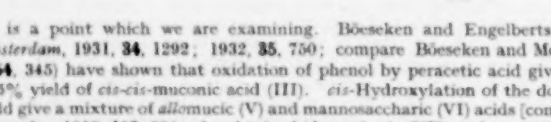
which would provide a closer parallel to the biochemical perhydroxylations of aromatic hydrocarbons.

As long ago as 1912, Dakin ("Oxidations and Reductions in the Animal Body," New York) pointed out that hydrogen peroxide, alone of all the known chemical oxidising agents, could bring about the same types of oxidation of a variety of compounds as do enzyme systems, and the widespread occurrence of catalase and peroxidases is a pointer to the importance of hydrogen peroxide in some types of biochemical oxidation. The oxidation of aromatic hydrocarbons by hydrogen peroxide was first reported by Leeds (*Ber.*, 1881, **14**, 975, 1382), who obtained phenol and oxalic acid from benzene, β-naphthol from naphthalene, and anthraquinone from anthracene. In recent years knowledge of the variety of conditions under which oxidations by hydrogen peroxide, and by peroxides and per-acids, can be effected has been widely extended (see, *e.g.*, Waters, *Ann. Reports*, 1945, **42**, 145) and the reaction mechanisms have been extensively studied. It was decided, therefore, to re-examine the oxidation of these hydrocarbons by hydrogen peroxide under varying conditions, and also to examine some more complex polycyclic hydrocarbons which are of interest on account of their carcinogenic activity. The present communication deals mainly with oxidations by hydrogen peroxide in *tert.*-butanol in presence of osmium tetroxide as catalyst. For comparison, some preliminary attention has also been devoted to oxidation by hydrogen peroxide alone, and by hydrogen peroxide catalysed by light, by chloride ions, and by haematin.

The osmium tetroxide reagent was introduced by Milas and Sussman (*J. Amer. Chem. Soc.*, 1936, **58**, 1302), who showed that olefins are not attacked by a solution of anhydrous hydrogen peroxide in *tert.*-butanol at room temperature until osmium tetroxide is added, whereupon they become oxidised to α-glycols. This reagent was found unsatisfactory in many of the cases which we studied on account of the low solubility of the polycyclic hydrocarbons in *tert.*-butanol. Acetone was therefore used as a solvent in conjunction with the Milas reagent. Treibs (*Ber.*, 1939, **72**, 7) had successfully used acetone as a solvent in catalysed hydrogen peroxide oxidations, but under the conditions which he used he did not apparently observe the formation of the cyclic peroxide of acetone (Wolffenstein, *Ber.*, 1895, **28**, 2265) which we regularly encountered. This appeared to have no significant influence on the course of the reaction. Parallel experiments on the oxidation of benzene by the Milas reagent led to the isolation of the same products, both in presence and in absence of acetone.

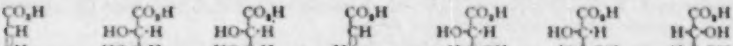
Results.

Benzene.—The hydroxylation of benzene by hydrogen peroxide in *tert.*-butanol catalysed by osmium tetroxide has already been reported by Milas and Sussman (*J. Amer. Chem. Soc.*, 1937, **59**, 2345) who obtained phenol in 23% yield. A somewhat higher yield (30%) of phenol was obtained by Milas (*ibid.*, p. 2342) when vanadium pentoxide was used as the catalyst. We also observed the formation of phenol when benzene was treated with the osmium tetroxide catalysed reagent, but if the experiment was continued for several months with excess of hydrogen peroxide a deposit separated, and this was identified as *allo*mucic acid; from the mother-liquors there were isolated also *meso*tartaric and oxalic acids. The transformation of benzene into a sugar acid is noteworthy. It is uncertain whether phenol is an intermediate or whether benzene becomes fully hydroxylated to a hexahydroxy*cyclo*hexane (I or II) which then undergoes ring-



fission. This is a point which we are examining. Böeseken and Engelberts (*Proc. Akad. Wetensch. Amsterdam*, 1931, **34**, 1292; 1932, **35**, 750; compare Böeseken and Metz, *Rec. Trav. chim.*, 1935, **54**, 345) have shown that oxidation of phenol by peracetic acid gives, with other products, a 35% yield of *cis-cis*-muconic acid (III). *cis*-Hydroxylation of the double bonds of this acid should give a mixture of *allo*mucic (V) and mannosaccharic (VI) acids [compare Behrend and Heyer, *Annalen*, 1919, **418**, 294, who obtained idosaccharic (VII) and mucic (VIII) acids by oxidation of *trans-trans*-muconic acid (IV) with sodium chlorate in presence of osmium tetroxide]. If a hexahydroxy*cyclo*hexane is formed in our conversion of benzene into *allo*mucic acid then this probably has the completely *cis*-configuration (I). The alternative configuration (II) which could arise from *cis*-addition in pairs of hydroxyl groups to the benzenoid double bonds (see

later) could give, on ring-fission, not only *allo*mucic acid (V) but also mucic (VIII), DL-manno-saccharic (VI and enantiomorph), and DL-talomucic (IX and enantiomorph) acids, and there was no indication of the formation of such a complex mixture of hexahydroxyadipic acids.

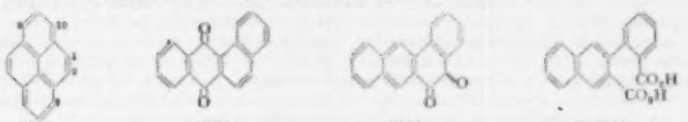


(III.) (V.) (VI.) (IV.) (VII.) (VIII.) (IX.)

This degradation of benzene by oxidation with the Milas reagent is of interest in connection with the metabolic conversion of benzene into *trans-trans*-muconic acid (IV), which is possibly an artefact formed by isomerisation of the *cis-cis*-acid (III) which should be the primary product of ring fission (Jaffé, *Z. physiol. Chem.*, 1909, **62**, 58; Drummond and Finar, *Biochem. J.*, 1938, **32**, 79; Bernhard and Greesley, *Helv. Chim. Acta*, 1941, **24**, 83). Such isomerisation is known to be readily effected (Grundmann and Trischmann, *Ber.*, 1936, **69**, 1755).

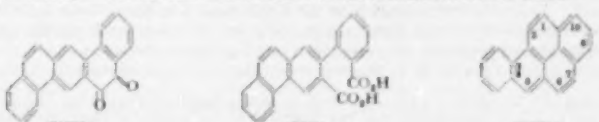
Naphthalene, Phenanthrene, Chrysene, Anthracene, and Pyrene.—The products formed from these hydrocarbons by oxidation with the Milas reagent call for little comment. In the case of naphthalene the only product isolated was phthalic acid, also obtained by Charrier and Moggi (*Gazzetta*, 1927, **57**, 736) by oxidation with hydrogen peroxide in an acid medium. Less extensive degradation occurs when naphthalene, α- or β-naphthol, or β-naphthaquinone is oxidised with peracetic -acid, *o*-carboxy*allo*cinnamic acid being formed in each case (Böeseken and Slooff, *Rec. Trav. chim.*, 1930, **49**, 100; Böeseken and von Königsfeldt, *ibid.*, 1935, **54**, 313).

Phenanthrene gave *cis*-**9** : 10-dihydroxy-**9** : 10-dihydrophenanthrene, phenanthraquinone, and diphenic acid. Charrier and Moggi (*loc. cit.*) had obtained diphenic acid by oxidising phenanthrene with hydrogen peroxide in boiling acetic acid, a result which we confirmed. Chrysene was oxidised to **1** : 2-chrysaquinone, and anthracene to **9** : 10-anthraquinone, which are the normal products of oxidation with chromic acid. Pyrene (X) was rapidly attacked and after about a week the products were separated into a mixture of quinones which appeared to be the **3** : 8- and **3** : 10-quinones which are the normal oxidation products. When the action of the Milas reagent was prolonged for a year the product was naphthalene-**1** : **4** : **5** : **8**-tetracarboxylic acid, characterised as its *methyl* ester. There was no evidence of attack at the **1** : 2-positions of pyrene, which are the positions exclusively attacked when pyrene is treated with osmium tetroxide in benzene–pyridine (Cook and Schoental, *loc. cit.*).



(X.) (XI.) (XII.) (XIII.)

1 : 2-*Benzanthracene and* **1** : 2-**5** : 6-*Dibenzanthracene.*—After a few days **1** : 2-benzanthracene gave the **3** : 4-quinone (XII) (isolated in 15% yield) and the **9** : 10-quinone (XI) (isolated in 20% yield). The *o*-quinone (XII), which is conveniently prepared in this way, is evidently formed through the intermediary of *cis*-**3** : 4-dihydroxy-**3** : 4-dihydro-**1** : 2-benzanthracene (Cook and Schoental, *loc. cit.*), a small amount of which was isolated by chromatography. When **1** : 2-benzanthracene was heated on the water-bath with the reagent acidic products were formed more rapidly than in the cold. Phthalic acid and 2-*phenylnaphthalene*-**3** : 2′-*dicarboxylic acid* (XIII) were isolated, and there was also evidence of the formation of keto-acids.



(XIV.) (XV.) (XVI.)

With **1** : 2-**5** : 6-dibenzanthracene the reaction took a similar course. On account of the low solubility of the hydrocarbon a more dilute solution was used, and the reaction was very

sluggish at room temperature. When the reactants were heated on the water-bath the dark red **1 : 2-5 : 6-dibenzanthra-3 : 4-quinone** (XIV) separated after a few days and was isolated in 35% yield. From the liquors the **9 : 10-quinone** was also isolated and, in addition, **2-phenylphenanthrene-3 : 2'-dicarboxylic acid** (XV), which was also obtained directly from the *o*-quinone (XIV) by oxidation with alkaline hydrogen peroxide.

3 : 4-*Benzpyrene* (XVI).—This was readily oxidised and the solution became deep-red. A mixture of quinones was then separated from other products of oxidation by chromatography on alumina. These quinones did not account wholly for the intensity of colour (noted also in the case of some of the other hydrocarbons). Possibly the high colour intensity was due to formation of hydroxylated quinones. Warren (*Biochem. J.*, 1943, **37**, 338), who studied the atmospheric oxidation of aqueous acetone solutions of **3 : 4**-benzypyrene in presence of ascorbic acid, also observed the formation of deeply coloured products in addition to known quinones.

Chromatography of the quinone fraction from benzpyrene resulted in only partial separation and the individual constituents were not isolated. Evidence was obtained, however, of the presence of the known **5 : 8**- and **5 : 10-quinones** (Vollmann *et al.*, *Annalen*, 1937, **531**, 1) and of a new *o*-quinone. The latter is probably **3 : 4-*benzpyrene*-6 : 7-*quinone***, which was prepared for comparative purposes by oxidation of the dihydroxydihydro-**3 : 4**-benzpyrene of Cook and Schoental (*loc. cit.*), and characterised by formation of a ***quinoxaline*** by reaction with *o*-phenylenediamine. The diol is believed to be the **6 : 7-diol**, although the alternative **1 : 2-structure** is not excluded (see numbering on formula XVI).

Oxidation of **1 : 2-*Benzanthracene* with *Hydrogen Peroxide* in *Absence of Osmium Tetroxide*.**—These experiments were carried out for comparison with the action of the Milas reagent. A solution of the hydrocarbon in acetone and *tert.*-butanol containing hydrogen peroxide remained unchanged for several weeks when kept in the dark. If methylamine hydrochloride was also present (used as a source of chloride ions) then oxidation took place and after two months a considerable proportion of the hydrocarbon had been oxidised to **1 : 2-benzanthra-9 : 10-quinone** (XI) and phthalic acid. There was no evidence of the formation of the **3 : 4-quinone** (XII). A similar result was obtained when haematin was used in place of methylamine hydrochloride.

Discussion.

The results of this investigation are mainly of interest on account of the additional evidence which they furnish as to the mechanism of oxidation by the Milas reagent, and they also perhaps provide one further span towards bridging the gap between biochemical and purely chemical oxidation of the aromatic hydrocarbons. Our earlier results with Criegee's osmium tetroxide reagent showed that it is possible to bring about selective chemical attack at positions in the molecules of polycyclic aromatic hydrocarbons which are not normally the most reactive. They also showed how it is possible to simulate the " perhydroxylation " reactions which are a characteristic feature of several of the biochemical oxidations. The positions attacked by osmium tetroxide are not those at which biochemical hydroxylation takes place, but in this connection it has been postulated that combination between the hydrocarbon and the oxidising enzyme may immobilise some of the more reactive centres in the hydrocarbon molecule.*

The diols and the related phenols which have been isolated in metabolic experiments represent only a small proportion of the hydrocarbon administered, and it is clear that most of the material undergoes more extensive degradation. Except in the case of benzene (see above) the products of this degradation have not been identified. Using **1 : 2-5 : 6-dibenzanthracene** containing isotopic carbon, Heidelberger and his collaborators (*Cancer*, 1948, **1**, 252, 261) have shown that acids are formed by ring-fission of the hydrocarbon and also that some of the material is completely oxidised to carbon dioxide. Metabolic studies by one of us (R. S.) with chrysene, **1 : 2-benzanthracene**, **1 : 2-5 : 6-dibenzanthracene**, and **3 : 4-benzpyrene** have likewise indicated that in all these cases acidic degradation products of the hydrocarbons are present in the excreta of the animals. To this extent oxidation by the Milas reagent imitates the metabolic oxidation, for prolonged treatment with the reagent always led to extensive conversion of the hydrocarbons into acidic degradation products, only some of which have been identified.

There remains the question as to how far the chemical perhydroxylations really follow the

* Berenblum and Schoental (*Cancer Res.*, 1943, **3**, 686) pointed out that in the cases of **1 : 2-benzanthracene** and **1 : 2-5 : 6-dibenzanthracene** the positions of the molecules where metabolic oxidation occurs are those at which sulphonation takes place *in the corresponding quinones*. This has been misinterpreted by Neish (*Biochem. J.*, 1948, **43**, 534) who states, incorrectly, that Berenblum and Schoental observed that benzanthracene and dibenzanthracene are metabolically attacked at points where sulphonation *of these hydrocarbons* occurs.

pattern of the corresponding biochemical processes. Osmium tetroxide oxidation of olefins and of phenanthrene has been shown by Criegee (*loc. cit.*) to give *cis*-diols through the intermediary of cyclic osmic esters. It is quite conceivable that metallic catalysts could function in a similar way in biochemical " perhydroxylation." But if it can be shown that one method of oxidation consistently gives *cis*-diols and the other *trans*-diols, then it is a reasonable inference that the reaction mechanisms are different. It is for this reason that great importance attaches to the determination of the configurations of the metabolic diols, and as already stated, evidence is accumulating that these are *trans*-isomers. An alternative possibility is that biochemical perhydroxylation is effected by free hydroxyl radicals, and there is much current opinion in favour of the view that free radicals play an important role in biological oxidations (see Waters, " Chemistry of Free Radicals," Oxford, 1946, p. 259; LuValle and Goddard, *Quart. Review Biol.*, 1948, **23**, 197).

Milas (*J. Amer. Chem. Soc.*, 1937, **59**, 2342) was inclined to regard oxidation by osmium tetroxide-catalysed hydrogen peroxide as involving attack by free hydroxyl radicals, formed by the action of perosmic acid on hydrogen peroxide, as in its dissociation by light (compare Spring, *Ann. Reports*, 1943, **40**, 108). That free hydroxyl radicals can oxidise benzene to phenol was shown by Stein and Weiss (*Nature*, 1948, **161**, 650; cf. Loebl, Stein, and Weiss, *J.*, 1949, 2074), who found phenol among the products of the action of *X*-rays on water and benzene. To this extent the Milas reagent produces the same result as free hydroxyl radicals. Moreover, Milas, Kurz, and Anslow (*J. Amer. Chem. Soc.*, 1937, **59**, 543) observed the oxidation of maleic acid to *meso*tartaric acid by hydrogen peroxide in presence of light and attributed this to addition of free hydroxyl radicals. This *cis*-addition rather than the *trans*-addition which might have been expected by such a mechanism excited no comment. Recently, Merz and Waters (*J.*, 1949, S 15) have shown that free hydroxyl radicals, produced by the action of ferrous salts on aqueous hydrogen peroxide, do not add to the double bond of maleic and fumaric acids. Hence the photochemical oxidation of maleic acid is not to be ascribed to the action of free hydroxyl radicals.

The same type of argument may be adduced to show that the perhydroxylation of double bonds by hydrogen peroxide in presence of osmium tetroxide is not due to the action of free hydroxyl radicals. It is true that in the Milas reagent part of the hydrogen peroxide is present as *tert.*-butyl hydroperoxide (compare Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205; Criegee and Dietrich, *Annalen*, 1948, **560**, 135), and that an alkyl hydroperoxide has been shown to break down to give free radicals (Robertson and Waters, *Trans. Faraday Soc.*, 1946, **42**, 201; *J.*, 1948, 1578). But the Milas reagent does not normally bring about the extensive degradations which Merz and Waters (*loc. cit.*) observed with free hydroxyl radicals; it does effect perhydroxylation of the double bonds in compounds of the maleic acid type, and moreover the method leads to *cis*-addition to the double bond (Milas and Sussman, *J. Amer. Chem. Soc.*, 1937, **59**, 2345; Milas, Sussman, and Mason, *ibid.*, 1939, **61**, 1844). It is clear, in fact, that the oxidation involves the intermediate formation of cyclic osmic esters, as in the Criegee method in which such esters are isolated.

Our own results with polycyclic hydrocarbons show that in part oxidation at a " potential " double bond takes place by the same mechanism. The isolation of *cis*-α-diols from phenanthrene and 1 : 2-benzanthracene, with no evidence of the presence of stereoisomeric *trans*-diols, points clearly to the intermediate formation of cyclic osmic esters. These diols undoubtedly represent the first stage also in the reactions which lead to 1 : 2-benzanthra-3 : 4-quinone (XII) and the acid (XIII) from 1 : 2-benzanthracene and the allied compounds (XIV) and (XV) from 1 : 2-5 : 6-dibenzanthracene. Moreover, the quite appreciable amounts of these products isolated indicate that the reactions by this route represent a considerable proportion of the whole. However, quite a different mechanism must operate in the oxidation of anthracene, 1 : 2-benzanthracene, and 1 : 2-5 : 6-dibenzanthracene to the 9 : 10-quinones (*e.g.*, XI), and in the oxidation of pyrene and 3 : 4-benzpyrene to their heteronuclear quinones. These oxidations may be due to the action of free hydroxyl radicals formed by dissociation of hydrogen peroxide, but there is no evidence bearing on this point, and judgment must be reserved. We are extending this work to study the effect on polycyclic hydrocarbons of free hydroxyl radicals and also of hydrogen peroxide in the presence of other catalysts. In this connection, it may be noted that Sequin (*Compt. rend.*, 1943, **216**, 667) obtained only the *trans*-α-glycol by oxidising *cyclo*hexene with hydrogen peroxide in acetone, in presence of selenium dioxide. A similar result was reported by Treibs (*Angew. Chem.*, 1939, **52**, 698) with pervanadic acid as catalyst.

Experimental.

General.—A solution of the hydrocarbon (0·001 g.-mol.) in acetone was treated with a stock solution of hydrogen peroxide (2—10 c.c.), prepared by diluting 90% hydrogen peroxide to 20—40% with *tert.*-butanol, and with a 1—2% solution of osmium tetroxide in *tert.*-butanol, so that the final concentration of the tetroxide varied between 0·01% and 0·5%. The solution was kept in a stoppered flask at room temperature in diffused light. Addition of the *tert.*-butanol solutions usually resulted in partial separation of the crystalline hydrocarbons, but the crystals redissolved in the course of the reaction. The colourless solutions slowly developed yellow or red colours of increasing intensity. There was usually an induction period when highly purified material was used. After the hydrogen peroxide initially added had been consumed the osmium tetroxide became reduced so that the solution became almost black. This colour was discharged by addition of more hydrogen peroxide solution. The rapidity with which this darkening of colour occurred furnished an index of the rate of oxidation of the hydrocarbons except in the cases of pyrene and 3 : 4-benzpyrene when very dark oxidation products were formed and the dark colour then persisted for some months. In view of the complex mixtures of oxidation products formed and the difficulty of isolating individual constituents a quantitative study was not attempted. Yields are recorded only when reaction products actually crystallised from solution.

For isolation of the products, any solid which had separated was collected, and the filtrate concentrated under reduced pressure at 40—50°. By this means solvents, osmium tetroxide, and volatile products were removed. Colourless crystals which collected in the still-head and condenser were identified as the trimeric cyclic peroxide of acetone, m. p. 94—95° (Wolffenstein, *loc. cit.*). Attempts to isolate the products without this preliminary concentration resulted in formation of dark colloidal suspensions of lower oxides of osmium, and as far as could be judged the distillation process did not bring about any alteration in the oxidation products.

The residue after distillation was a yellow or brownish viscous oil, which was treated with dilute sodium hydrogen carbonate solution and extracted with benzene. Dark resinous material remained insoluble in both phases, but dissolved when sodium hydroxide solution was added, after removal of the sodium hydrogen carbonate layer. Acidification of the dark sodium hydroxide extracts gave brownish material which did not crystallise and gave no crystalline derivatives by reductive methylation or acetylation.

The benzene extracts were submitted to chromatography on alumina and were thus separated into unchanged hydrocarbon, diol (in two cases), and quinones. In all cases highly coloured zones of strongly adsorbed material were visible on the upper part of the column, but pure products could not be obtained after these were eluted with acidified alcohol.

The sodium hydrogen carbonate extract was acidified, and the resulting acids separated by fractional crystallisation from various solvents or by vacuum distillation of their methyl esters, formed by treatment with ethereal diazomethane.

Benzene.—Two parallel experiments were made. In one, the reaction was carried out in acetone solution, as in the other cases recorded in this paper. In the other, *tert.*-butanol alone was used as solvent. Oxidation took place more rapidly in acetone solution, but in both cases the same products were isolated. The reaction mixtures, prepared in each case by using 10 c.c. of benzene, became yellow in a few days and phenol was detected by its smell, by the preparation of tribromophenol, m. p. 93°, from a sample of distillate, and by the blue colour given with 2 : 6-dichloroquinonechloroimide in neutral or alkaline solution (Porteous and Williams, *Biochem. J.*, 1949, **44**, 56).

The colour of the solution of reactants deepened on storage, but after some months, during which several additions of hydrogen peroxide solution were made, the colour became pale yellow and a white precipitate was formed. This (35 mg.) was recrystallised from hot water and formed a microcrystalline powder which decomposed at 197°. Analysis showed the compound to be a tetrahydroxyadipic acid (Found: C, 34·0; H, 5·0. Calc. for $C_6H_{10}O_8$: C, 34·3; H, 4·8%). Its ethyl ester, prepared by heating it under reflux with ethanol containing a few drops of concentrated hydrochloric acid, had m. p. *ca.* 150°. These data are in approximate agreement with those given for *allo*mucic acid by Posternak (*Helv. Chim. Acta*, 1935, **18**, 1283) (acid, m. p. 197—198°; ethyl ester, m. p. 153—154°) and by Lapsley, Robertson, and Patterson (*J.*, 1940, 802) (acid, m. p. 199—200°; ethyl ester, m. p. 155°). Through the kindness of Mr. J. Robertson, who generously gave us a sample of *O*-tetra-acetyl*allo*mucic acid prepared by the method described by himself and his collaborators, we have been able to establish that our oxidation product is in fact *allo*mucic acid. The methyl ester of our acid had m. p. 170° and gave an *O*-tetra-acetyl derivative, m. p. 204—206°. The m. p.s of the acid and its three derivatives were not depressed by mixing with the acid (prepared by acid hydrolysis of the authentic *O*-tetra-acetyl*allo*mucic acid) and its corresponding derivatives. On the other hand, a mixture of the methyl ester of the tetra-acetate of our acid and methyl *O*-tetra-acetylmucate, m.p. 196—197° (Simon and Guillaumin, *Compt. rend.*, 1924, **179**, 1324), melted at 180—196°. Pure *methyl allomucate* formed transparent prisms (from methanol), m. p. 175° after softening (Found: C, 40·6; H, 5·9. $C_8H_{14}O_8$ requires C, 40·3; H, 5·9%). *Methyl O-tetra-acetylallomucate*, prepared from methyl *allo*mucate by acetylation with acetic anhydride, formed transparent rhombic prisms, m. p. 205—206° (Found: C, 47·3; H, 5·6. $C_{16}H_{22}O_{12}$ requires C, 47·3; H, 5·5%).

In another experiment, a mixture of benzene (10 c.c.) and acetone (10 c.c.) was treated with 2% osmium tetroxide (2 c.c.) and 40% hydrogen peroxide (60 c.c.), both in *tert.*-butanol. After nine months the filtered solution was concentrated under reduced pressure at 40—50°. A solution in water of the residual oil was partly neutralised with sodium carbonate and the solution heated under reflux for 2½ hours with *p*-bromophenacyl bromide (0·5 g.) in ethanol (10 c.c.). After concentration and cooling the resulting *p*-bromophenacyl ester was recrystallised from ethanol and formed glistening leaflets, m. p. 198—200°. This was shown to be *p-bromophenacyl mesotartrate*, a sample of which was prepared from authentic *meso*tartaric acid and had m. p. 198—200°, alone or mixed with the above product (Found: C, 44·25; H, 3·2. $C_{20}H_{14}O_8Br_2$ requires C, 44·1; H, 3·0%).

In yet another experiment the filtrate from the crude *allo*mucic acid was concentrated under reduced pressure, the residue dissolved in water and almost neutralised with sodium hydroxide, and the boiling solution then treated with saturated calcium acetate solution. Without cooling, the white precipitate was collected, washed, and dried. It was shown by titration with warm acid permanganate solution to consist of calcium oxalate. The filtrate was concentrated and gave large crystals which were redissolved in hot water; the solution was acidified and then extracted with ether. After removal of the ether the residue was treated with ethereal diazomethane and gave colourless prisms, m. p. 111—112°, shown by mixed m. p. to consist of methyl *meso*tartrate.

In yet another experiment, the crude mixture of acids, freed from volatile substances, was esterified with diazomethane and the esters were distilled. The fraction, b. p. 110°/0·3 mm., gave again methyl *meso*tartrate. The higher-boiling esters could not be separated; much of the material underwent decomposition during distillation. Although the hydroxyl groups of *meso*tartaric acid were not affected by diazomethane it may be noted that Schmidt and Zeiser (*Ber.*, 1934, **67**, 2120) found that tartaric and other hydroxy-acids undergo etherification as well as esterification with diazomethane.

Naphthalene.—A solution of the hydrocarbon (5 g.) in acetone (25 c.c.) with 1% osmium tetroxide in *tert.*-butanol (2·5 c.c.) and hydrogen peroxide solution (15 c.c.) immediately became yellow and oxidation proceeded rapidly; further quantities of hydrogen peroxide solution were added as required. After 18 days the solution was worked up in the usual way. The acidic fraction was mainly soluble in water. It was extracted with ether, recovered from the extract, and recrystallised several times from ethyl acetate and aqueous methanol. The resulting acid had m. p. *ca.* 200°, and on sublimation gave long needles, m. p. 137°, shown by mixed m. p. to be phthalic anhydride.

When the solution of the reactants was worked up after shorter periods there were shown to be present phenolic material and also coloured neutral products, probably naphthaquinones (compare Milas, U.S.P., 2,395,638).

Phenanthrene.—The hydrocarbon (3 g.) in acetone (15 c.c.) was treated with the Milas reagent (2 c.c. of osmium tetroxide solution and 10 c.c. of hydrogen peroxide solution) at room temperature. Further additions of hydrogen peroxide solution were made from time to time, about 60 c.c. of a 20% solution being used in all. After 26 days the red solution was concentrated *in vacuo* and then deposited crystals (55 mg.), m. p. 204—206°, which were shown to consist of phenanthraquinone. The filtrate was worked up in the usual way, and on passing the benzene solution through a column of alumina there were obtained from the first benzene filtrate some unchanged phenanthrene and then a fraction which gave fine colourless needles (from light petroleum) of *cis*-9 : 10-dihydroxy-9 : 10-dihydrophenanthrene (25 mg.), m. p. 178° alone or mixed with a specimen prepared as described by Criegee, Marchand, and Wannowius (*Annalen*, 1942, **550**, 99). A yellow zone was cut from the alumina column and gave on elution with benzene more phenanthraquinone, m. p. 206—207°.

The acidic fraction was repeatedly crystallised from aqueous methanol and ethyl acetate. This gave colourless prisms, m. p. 228—230°, shown by mixed m. p. to be diphenic acid. Identification was completed by conversion into the anhydride, m. p. and mixed m. p. 217°. The sodium hydroxide extract on acidification gave a product which was purified by passing its benzene solution through a column of alumina. This gave a small amount of 9-phenanthrol, m. p. and mixed m. p. 148°.

Chrysene.—In this case reaction was slow, but the hydrocarbon in suspension (using 330 mg. in 50 c.c. of acetone) dissolved during the course of 3 weeks. The red solution was concentrated *in vacuo* and gave red needles of 1 : 2-chrysaquinone, m. p. 237—238°, not depressed by mixing with an authentic specimen. Small amounts of acidic and other products were also formed.

Anthracene.—The hydrocarbon (100 mg.) in acetone (10 c.c.) was treated with 1% osmium tetroxide solution (1 c.c.) and 20% hydrogen peroxide solution (2 c.c.). After 4 days long needles of anthraquinone began to separate (m. p. and mixed m. p. 275°). In another experiment 250 mg. of anthracene gave, after 4 months, 170 mg. of anthraquinone and traces of unidentified acidic products.

Pyrene.—A solution of this hydrocarbon (350 mg.) in acetone (10 c.c.) became pink immediately on the addition of the Milas reagent. After a week the deep-red solution was worked up. Chromatography of the benzene extract led to recovery of some unchanged hydrocarbon and gave several coloured bands. Chloroform eluted a mixture of quinones, which were not completely separated by repeated chromatography in benzene. The colours given by the various fractions with concentrated sulphuric acid indicated the presence of the 3 : 8- and 3 : 10-quinones (Vollmann *et al.*, *loc. cit.*). There was no definite evidence of the presence of the 1 : 2-quinone.

In another experiment the solution of reactants was kept for about a year. The deep colour slowly faded and a pale yellow solid was deposited. This was recrystallised from much ethanol and then sublimed under reduced pressure, giving yellowish needles of naphthalene-1 : 4 : 5 : 8-tetracarboxylic dianhydride, m. p. above 360°. Treatment of the silver salt with methyl iodide gave the *methyl* ester as colourless leaflets, m. p. 196—198°, not depressed by mixture with a sample similarly prepared from Cook and Hewett's tetracarboxylic acid (*J.*, 1933, 405) (Found: C, 60·2; H, 4·7. $C_{18}H_{16}O_8$ requires C, 60·0; H, 4·5%).

1 : 2-*Benzanthracene.*—(*a*) A solution of the hydrocarbon (0·5 g.) in acetone (20 c.c.) was treated with 40% hydrogen peroxide (2 c.c.) and 1% osmium tetroxide (1 c.c.), both in *tert.*-butanol. The solution soon became red and in the course of 3—4 days red crystals separated (80 mg.). After crystallisation from chloroform these had m. p. 260—262°, not depressed by admixture with a sample of the quinone (XII) prepared by chromic acid oxidation of *cis*-3 : 4-dihydroxy-3 : 4-dihydro-1 : 2-benzanthracene. The product gave a purple solution in concentrated sulphuric acid, in agreement with Fieser and Dietz (*J. Amer. Chem. Soc.*, 1929, **51**, 3141). The quinone reacted with *o*-phenylenediamine in acetic acid solution to give the *quinoxaline* as pale yellow needles, m. p. 256—257° (Found: C, 86·9; H, 4·3. $C_{24}H_{14}N_2$ requires C, 87·2; H, 4·3%).

The mother-liquors from which this quinone had been separated were worked up in the normal manner. Chromatography of the benzene extract showed that very little unchanged hydrocarbon was present. The benzene eluate gave 1 : 2-benzanthra-9 : 10-quinone (XI) (120 mg.) as orange needles, m. p. 167—168°. Chromatographic purification of the material from the mother-liquors of this gave a

small amount of *cis*-3 : 4-dihydroxy-3 : 4-dihydro-1 : 2-benzanthracene, m. p. 201—205°, not depressed by admixture with a sample prepared as described by Cook and Schoental (*loc. cit.*).

The acidic products insoluble in water (*i.e.*, precipitated by acidification of the sodium hydrogen carbonate extract) were recrystallised several times from ethyl acetate and gave a small amount of colourless crystals, m. p. 245°. This acid was shown to be identical with *2-phenylnaphthalene-3 : 2'-dicarboxylic acid* (XIII), colourless prisms, m. p. 249—250° (from ethyl acetate), formed by oxidation of 1 : 2-benzanthra-3 : 4-quinone (XII) with alkaline hydrogen peroxide (compare Weitz, Schobbert, and Seibert, *Ber.*, 1935, **68**, 1163), and the same acid was also formed from the quinone (XII) by treatment with the Milas reagent for several weeks (Found : C, 74·3; H, 4·1. $C_{18}H_{10}O_4$ requires C, 74·0; H, 4·1%). Its *methyl ester*, prepared by heating it with hydrochloric acid in methanol, formed colourless plates, m. p. 86—87·5° (Found : C, 75·05; H, 5·0. $C_{20}H_{14}O_4$ requires C, 75·1; H, 5·0%).

In another experiment on the oxidation of benzanthracene by the Milas reagent the acidic products were esterified with diazomethane and distilled *in vacuo*. The first fraction, b. p. 90—100°/0·3 mm., was mostly methyl phthalate, identified by conversion into the anhydride. The fraction, b. p. 120—180°/0·3 mm., gave on hydrolysis the acid (XIII). Treatment of the crude acid mixture with 2 : 4-dinitrophenylhydrazine gave a small amount of solid, indicating the presence of keto-acids, but a pure substance could not be isolated.

(*b*) 1 : 2-Benzanthracene (0·5 g.) in acetone (20 c.c.) was treated with 50% hydrogen peroxide in *tert.*-butanol (3 c.c.) and methylamine hydrochloride (140 mg.). The mixture was kept in the dark for 2 months and gave 1 : 2-benzanthra-9 : 10-quinone (170 mg.) and acidic products from which phthalic acid was isolated by distillation of the esterified material.

(*c*) A similar experiment with haematin (prepared from haemin as described by Fischer *et al.*, *Z. physiol. Chem.*, 1930, **193**, 156) in place of methylamine hydrochloride gave 1 : 2-benzanthra-9 : 10-quinone in 50% yield and some phthalic acid.

1 : 2-5 : 6-*Dibenzanthracene*.—The slight solubility of this hydrocarbon necessitated the use of a very dilute solution and the reaction was exceedingly slow at room temperature. It was therefore accelerated by heating. The hydrocarbon (500 mg.) in acetone (50 c.c.) was treated with 50% hydrogen peroxide (10 c.c.) and 1% osmium tetroxide (10 c.c.), both in *tert.*-butanol, and the solution was heated at 70° for 3—4 days. The purple crystals which separated (160 mg.) were recrystallised from acetic acid and formed dark red needles, m. p. 325°. This substance was shown to be identical with 1 : 2-5 : 6-dibenzanthra-3 : 4-quinone (XIV) prepared as described by Stephenson (*J.*, 1949, 2620), who gives m. p. 327—329° (compare Cook, *J.*, 1933, 1594). Concentration of the original filtrate gave a yellow solid which crystallised from benzene in orange-yellow needles, m. p. 246°, consisting of 1 : 2-5 : 6-dibenzanthra-9 : 10-quinone (Clar, *Ber.*, 1929, **62**, 350).

The sodium hydrogen carbonate fraction on acidification gave a solid precipitate which after several recrystallisations formed a cream microcrystalline powder (from acetone), m. p. 307—309°. This was 2-phenylphenanthrene-3 : 2'-dicarboxylic acid (XV), a sample of which was prepared for comparison by oxidation of the quinone (XIV) with hydrogen peroxide in boiling methanolic sodium hydroxide (compare Weitz *et al.*, *loc. cit.*). The resulting acid had m. p. 316°, and did not depress the m. p. of the acid obtained by oxidising the hydrocarbon with the Milas reagent, or that obtained by another route by Stephenson (*loc. cit.*), who gives m. p. 311—313°. For characterisation, the *methyl* ester of (XV) was prepared by the Fischer–Speier method. It formed almost colourless leaflets (from ethanol), m. p. 144—145° (Found : C, 77·3; H, 5·1. $C_{21}H_{16}O_4$ requires C, 77·8; H, 4·9%).

3 : 4-*Benzpyrene* (XVI).—The oxidation of this hydrocarbon with the Milas reagent proceeded as with pyrene. Chromatography on alumina of the benzene extract after concentration (a large volume of benzene was required) gave a red zone. The column was cut and this was eluted with chloroform. Repeated chromatography from benzene of the concentrated eluate resulted in partial separation into a lower (yellow) band and an upper (red) band. These were cut, eluted with chloroform, and concentrated. The residue from the yellow band gave a cherry-red solution in concentrated sulphuric acid, whereas that from the red band gave an olive-brown solution. These colours are consistent with the view that the yellow quinone is the 5 : 10-quinone and the red quinone the 5 : 8-quinone obtained by Vollmann *et al.* (*loc. cit.*) by chromic acid oxidation of 3 : 4-benzpyrene (XVI).

Some of the fractions from the chromatogram gave a deep violet colour with sulphuric acid and reacted with *o*-phenylenediamine in acetic acid to give a yellow precipitate, indicating an *o*-quinone. For comparison, the dihydroxydihydro-3 : 4-benzpyrene of Cook and Schoental (*loc. cit.*) was oxidised with chromic acid and the resulting *quinone*, probably the 6 : 7-quinone, crystallised from glacial acetic acid. It formed orange-red needles, m. p. 240° (decomp.), and gave the expected deep-violet solution in concentrated sulphuric acid (Found : C, 85·0; H, 3·6. $C_{20}H_{10}O_2$ requires C, 85·1; H, 3·55%). The *quinoxaline*, prepared by treatment with *o*-phenylenediamine in acetic acid, formed small yellow needles, m. p. 318° (decomp.), not depressed by admixture with the precipitate similarly formed from fractions of the chromatogram (Found : C, 87·8; H, 4·2; N, 7·8. $C_{26}H_{14}N_2$ requires C, 88·1; H, 4·0; N, 7·9%).

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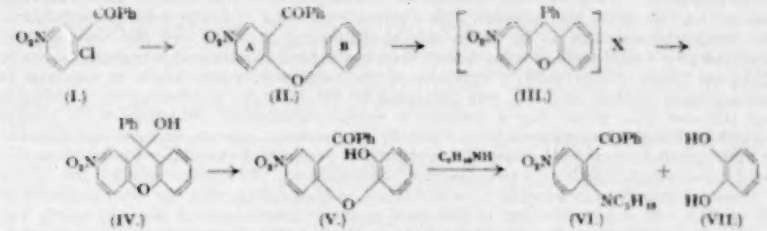
13. ortho-*Hydroxylation of Phenols. A New Case of the Smiles Rearrangement.*

By J. D. Loudon, J. R. Robertson, J. N. Watson, and (in part) (Miss) S. D. Aiton.

The potassium salts of various phenols condense with 2-chloro-5-nitrobenzophenone to form *5-nitro-2-aryloxybenzophenones* which with concentrated sulphuric acid afford solutions of the corresponding 9-phenylxanthylium sulphates. These solutions yield (*a*) derivatives of 9-phenylxanth-hydrol when treated with water, or (*b*) *5-nitro-2-o-hydroxyaryloxybenzophenones*, *e.g.*, (V), when treated with acetic acid and hydrogen peroxide. Compounds of type (V) react with piperidine to give catechol derivatives and *5-nitro-2-piperidinobenzophenone*, form unstable, covalent sodium derivatives, and in particular cases rearrange in alkaline solution, the nitrobenzophenone residue migrating to the second oxygen atom of the catechol system, *e.g.*, (X) ⟶ (XI).

The following investigation was undertaken to test the practicability of the reaction scheme illustrated by (I)—(VII) and to define the respects requiring particular study in order to achieve a general development. Condensation between 2-chloro-5-nitrobenzophenone (I) and the potassium salts of various phenols afforded the aryl *ethers*, *e.g.*, (II), in satisfactory yields and, in most cases, these were converted smoothly into 9-phenylxanthylium salts by dissolution in cold concentrated sulphuric acid. The corresponding *xanth-hydrols*, *e.g.*, (IV), were obtained by pouring the solutions into water. This cyclisation process is analogous to that already described for the formation of thioxanthen derivatives (Loudon *et al.*, *J.*, 1941, 747) and, since it depends on nucleophilic reactivity in ring B (cf. (II)), was less readily accomplished in cases where this ring was nitrated.

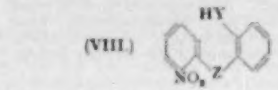


Quint and Dilthey (*Ber.*, 1931, **64**, 2082) have shown that 9-phenylxanthylium perchlorate is oxidised by hydrogen peroxide in acetic acid to 2-*o*-hydroxyphenoxybenzophenone (V; H for (NO_2)). Similar oxidation of *perchlorates* derived from our 2-nitro-9-phenylxanth-hydrols gave mainly neutral products, presumably *peroxides* of the type encountered by Dilthey (*loc. cit.*). In a number of cases, however, the required catechol derivatives, *e.g.*, (V), were very readily obtained by oxidising the xanth-hydrol in sulphuric–acetic acid, and the process gave excellent results with 9-phenylxanth-hydrol itself. Consequently, in these cases a simple and almost quantitative conversion of the phenol derivatives (II; ring B = phenyl, or *o*-, *m*-, or *p*-tolyl) into the catechol derivatives, *e.g.*, (V), was achieved by dissolving the former in concentrated sulphuric acid, diluting the solution with acetic acid and adding hydrogen peroxide. That the pyrylium ring opens in the sense shown was confirmed by the identity of the methylation product of (V) with the condensation product obtained from (I) and guaiacol.

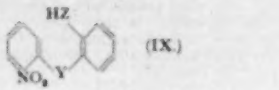
The final stage of the reaction scheme, *viz.*, liberation of the catechol from its aryl ether, was not examined extensively. The scission of *o*- or *p*-nitrated diaryl ethers by means of piperidine is well known (Le Fèvre, Saunders, and Turner, *J.*, 1927, 1168; Groves, Turner, and Sharp, *J.*, 1929, 512) and we have limited our present inquiry to a few test cases using this reagent. Catechol, **3**:4-dihydroxytoluene, and **4**-hydroxy-**3**-methoxytoluene were isolated from (V), (XI), and (XI*a*), respectively, and in each case *5-nitro-2-piperidinobenzophenone* was also produced.

Since it is part of our project to study the extension of the process through renewed cyclisation at the catechol stage (V), with or without alkylation of the free phenolic group, it became necessary to examine the behaviour of the catechol derivatives particularly towards alkaline reagents. Smiles and his collaborators have shown (for summary and references, cf. *Ann. Reports*, 1939, **36**, 197) that the different donor-capacities in dissimilar atoms Y and Z

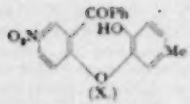
constitute an important factor in the rearrangement of (VIII) to (IX). Different donor-capacities will also exist where Y and Z represent atoms of the same element dissimilarly situated in the molecule. This condition and other essential features for rearrangement are present in the isomers (X) and (XI). Experiment indeed showed that when (X) was dissolved in aqueous alkali it was almost completely rearranged to the compound which had already been obtained by hydroxylating the *p*-tolyl ether (II; ring B = *p*-tolyl) and which, accordingly, has the formula (XI). For this reason also methylation of either (X) or (XI) by methyl sulphate in alkali afforded the same *methyl ether* (XIa), which was identified by scission with piperidine to



(VIII.)

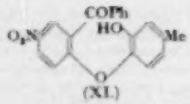


(IX.)



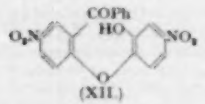
(X.)

(Xa; MeO for HO.)



(XI.)

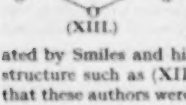
(XIa; MeO for HO.)



(XII.)

4-hydroxy-3-methoxytoluene as already mentioned. On the other hand, methylation without rearrangement was effected by means of diazomethane, which gave (Xa) and (XIa) from (X) and (XI), respectively, the *ether* (Xa) being identified by its formation from (I) and 3-hydroxy-4-methoxytoluene. There was also evidence of rearrangement in the case of the *nitrocatechol* derivative (XII) which was prepared from *p*-nitrophenol *via* 2 : 7-*dinitro*-9-*phenylxanth-hydrol*. The compound appeared to be isomerised by dissolution in alkali and the same change, displayed as a double melting point, occurred on heating the substance in soft-glass but not in hard-glass tubes. Unfortunately, synthesis of the compound, which would be expected as rearrangement product of (XII), was prevented by the difficulty of effecting the cyclisation step (II) ⟶ (III) where ring B contains a *m*-nitro-substituent. Nitration of (I) yielded 2-*chloro*-3′ : 5-*dinitrobenzophenone* from which by condensation with *m*- and *p*-cresol, followed by hydroxylation, there were prepared respectively 3′ : 5-*dinitro*-2-(2-*hydroxy*-5-*methylphenoxy*)- and 3′ : 5-*dinitro*-2-(2-*hydroxy*-4-*methylphenoxy*)-*benzophenone*. In alkaline solution the former of these compounds was isomerised to the latter, corresponding with the rearrangement of (X) to (XI). It is probable that in the cases examined rearrangement is not complete but reaches an equilibrium point. This is suggested by the fact that the products of rearrangement, like the synthetic samples when recovered from solution in alkali, melt lower and less sharply than the pure compounds.

In the course of these experiments in alkaline media it was noted that the sodium and potassium salts of the catechol derivatives of type (V) were only sparingly soluble in aqueous alkali. Further examination showed that in these compounds the metal is present in the covalent condition. The compounds were obtained as yellow crystalline solids of low melting points; they were sparingly soluble in cold water and were hydrolysed to the metal-free compounds by warm water; they dissolved readily in warm benzene or chloroform, losing water and giving orange-coloured solutions from which less coloured, lower hydrated forms separated on cooling. Their general instability made it difficult to secure consistent and reliable analytical data. Quint and Dilthey (*loc. cit.*) describe a yellow sodium salt of 2-(*o*-hydroxyphenoxy)benzophenone and re-examination of this compound showed that here too the metal is covalently bound. Since corresponding salts of 2-hydroxydiphenyl ether are of the normal type, the carbonyl group of the present compounds appears to take part in the covalent linking of the metal. By analogy with the covalent alkali derivatives of salicylideneacetophenone and related compounds investigated by Smiles and his colleagues (cf. Dvorkovitz and Smiles, *J.*, 1938, 2022), this suggests a structure such as (XIII) containing a strainless 9-membered ring. It is noteworthy, however, that these authors were unable to find evidence of stable ring structures of this type containing more than eight members.



(XIII.)

Experimental.

2-*Chloro*-3′ : 5-*dinitrobenzophenone*.—Solutions of 2-chloro-5-nitrobenzophenone (4·4 g.) (Fries, *Annalen*, 1927, **454**, 287) and potassium nitrate (1·7 g.) in the requisite quantity of concentrated

sulphuric acid were mixed and, after 12 hours at room temperature, the mixture was poured into ice-water. The *product* formed colourless plates, m. p. 177°, from acetic acid (Found: C, 51·0; H, 2·3; N, 9·3. $C_{13}H_7O_4N_2Cl$ requires C, 50·9; H, 2·3; N, 9·1%).

For the preparation of the aryloxybenzophenones the chloronitrobenzophenone (1 mol.) was added to a fused mixture of the appropriate phenol (1—2 mols.) and its potassium salt (1·2 mols.). Gentle heating initiated an exothermic reaction which was allowed to complete itself and after further brief heating (in all 15—20 minutes) the mass was cooled and treated with a dilute solution of sodium hydroxide. The solidified product was crystallised from acetic acid, diluted if necessary. In this way the tabulated compounds were prepared from 2-chloro-5-nitrobenzophenone or from 2-chloro-3′,5-dinitrobenzophenone.

Aryl group.	M. p.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
5-Nitro-2-aryloxybenzophenones.						
Phenyl	150°	$C_{19}H_{13}O_4N$	71·8	4·3	71·5	4·1
o-Tolyl	121—122	$C_{20}H_{15}O_4N$	72·2	4·3	72·1	4·5
m-Tolyl	106	$C_{20}H_{15}O_4N$	72·0	4·6	72·1	4·5
p-Tolyl	129	$C_{20}H_{15}O_4N$	72·1	4·3	72·1	4·5
o-Methoxyphenyl	132	$C_{20}H_{15}O_5N$	72·0	4·5	72·1	4·5
m-Chlorophenyl	117	$C_{19}H_{12}O_4NCl$	64·9	3·5	64·5	3·4
p-Chlorophenyl	118	$C_{19}H_{12}O_4NCl$	64·8	3·3	64·5	3·4
m-Nitrophenyl	116—117	$C_{19}H_{12}O_6N_2$	62·8	3·5	62·6	3·3
p-Nitrophenyl	106	$C_{19}H_{12}O_6N_2$	62·6	3·2	62·6	3·3
2-Methoxy-5-methylphenyl	120	$C_{21}H_{17}O_5N$	69·7	4·8	69·4	4·7
β-Naphthyl	137—138	$C_{23}H_{15}O_4N$	74·75	4·2	74·8	4·1
3′ : 5-Dinitro-2-aryloxybenzophenones.						
Phenyl	73	$C_{19}H_{12}O_6N_2$	62·3	3·7	62·6	3·3
m-Tolyl	123	$C_{20}H_{14}O_6N_2$	63·8	3·6	63·5	3·7
p-Tolyl	184	$C_{20}H_{14}O_6N_2$	63·5	3·8	63·5	3·7

2-Nitro-9-phenylxanthydrol (IV), m. p. 184° [from benzene–petroleum (b. p. 60—80°)] (Found: C, 71·55; H, 4·1. $C_{19}H_{13}O_4N$ requires C, 71·5; H, 4·1%), was prepared by dissolving 5-nitro-2-phenoxybenzophenone in cold concentrated sulphuric acid and, after an hour at room temperature, pouring the red solution into ice-water. The *xanthylium perchlorate*, m. p. 211° (Found: C, 56·7; H, 3·4. $C_{19}H_{12}O_6N{\cdot}ClO_4$ requires C, 56·7; H, 3·0%), was obtained as orange-red crystals when perchloric acid (0·11 g.) was added to a warm solution of the xanthydrol (0·2 g.) in acetic acid (5·5 c.c.).

In similar fashion the following were prepared from the appropriate 5-nitro-2-aryloxybenzophenone: *2-nitro-9-phenyl-6-methylxanthydrol*, m. p. 186° (Found: C, 72·2; H, 4·5. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%); *2-nitro-9-phenyl-7-methylxanthydrol*, m. p. 163° (Found: C, 72·1; H, 4·7. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%) [the derived *perchlorate* had m. p. 260° (decomp.) (Found: C, 57·5; H, 3·5. $C_{20}H_{14}O_4N{\cdot}ClO_4$ requires C, 57·7; H, 3·6%)]; *2-nitro-9-phenyl-7 : 8-benzxanthydrol*, m. p. 240° (Found: C, 74·6; H, 4·3. $C_{23}H_{15}O_4N$ requires C, 74·8; H, 4·1%); and *2 : 7-dinitro-9-phenylxanthydrol*, m. p. 194—195° (Found: C, 62·8; H, 3·2. $C_{19}H_{11}O_6N_2$ requires C, 62·6; H, 3·3%). Cyclisation in the last case was completed by heating a solution of the ketone (2 g.) in concentrated acid (25 c.c.) at 120—130° for 20 minutes, but even these conditions failed to achieve a satisfactory cyclisation with 5-nitro-2-*m*-nitrophenoxybenzophenone which was recovered largely unchanged although the red colour of the solution indicated partial formation of the xanthylium salt.

2-o-Hydroxyphenoxybenzophenone.—A solution of 9-phenylxanth-hydrol (1 g.) in concentrated sulphuric acid (1 c.c.) was diluted with acetic acid (11 c.c.), and hydrogen peroxide was added dropwise and with shaking. The initial yellow colour of the solution rapidly changed to orange-red which gradually faded to a pale yellow (*ca.* 1 hour). At this stage the mixture, in which some colourless flaky crystals appeared, was poured into water. The partly solid gum solidified when rubbed with ethanol, yielding 2-*o*-hydroxyphenoxybenzophenone (0·95 g.), m. p. 103—104°, from ethanol (Quint and Dilthey, *loc. cit.*, give m. p. 104°).

Sodium derivative. The above compound dissolved in warm dilute sodium hydroxide to form a yellow solution from which, on cooling, the sodium salt separated as beautiful yellow leaflets (Found: C, 53·8; H, 5·8. Calc. for $C_{19}H_{13}O_3Na,6H_2O$: C, 54·3; H, 5·95%). When slowly heated these sintered at 80—90° and melted quite sharply at 135—136°; when suddenly exposed to a temperature of 100—110° they rapidly liquefied, re-solidified, and again melted at 135°. They appeared to be insoluble in cold water but when shaken with warm water gave first a turbid and then a clear solution from which, on cooling, needles of the parent compound, m. p. and mixed m. p. 102—104°, were deposited. On the other hand, when heated with benzene they dissolved, water being liberated, and the hot filtered solution deposited the *trihydrate* as a mass of fine colourless needles which gave a clear yellow melt at 135—136° and did not melt when plunged into a bath at 110° (Found: C, 62·9; H, 4·8. $C_{19}H_{13}O_3Na,3H_2O$ requires C, 62·3; H, 5·2%).

5-Nitro-2-o-hydroxyphenoxybenzophenone (V).—(i) A suspension of 5-nitro-9-phenylxanthylium perchlorate (1 g.) in acetic acid (10 c.c.) was treated with 30% hydrogen peroxide (2 c.c.). The colour of the salt was gradually discharged and after 12 hours at room temperature the colourless crystalline solid (*A*) was collected, and the filtrate, on dilution with water gave a flocculent precipitate. The latter, which was completely soluble in dilute sodium hydroxide, afforded the compound (V) (cf. below), and was converted by reaction with methyl sulphate in alkaline solution into 5-nitro-2-*o*-methoxyphenoxybenzophenone, m. p. and mixed m. p. 130—132°. The crystalline solid (*A*), which was the main product of the reaction, was insoluble in cold dilute alkali, liberated iodine from a solution of

potassium iodide and was probably a *peroxide* derived from the xanth-hydrol (cf. Quint and Tolthey, *loc. cit.*); it had m. p. 180° (decomp.) (from acetic acid) (Found: C, 68·1; H, 4·2. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 3·9%). (ii) 5-Nitro-2-phenoxybenzophenone (2·6 g.) was dissolved in cold concentrated sulphuric acid (4·2 c.c.) and, after 30 minutes, acetic acid (26 c.c.) was added. With vigorous stirring but without external cooling, hydrogen peroxide (6 c.c.) was then added fairly rapidly (5 minutes) and the whole was kept at room temperature for 3 hours. The mixture was then poured into water, giving the required *product* (V) in almost quantitative yield. It formed faintly yellow needles, m. p. 159°, from ethanol (Found: C, 68·2; H, 4·1. $C_{19}H_{13}O_4N$ requires C, 68·1; H, 3·9%).

5-Nitro-2-(2-hydroxy-4-methylphenoxy)benzophenone (XI) was similarly obtained (i) from 2-nitro-7-methylxanthylium perchlorate which also yielded mainly a *peroxide*, m. p. 210° (decomp.) (Found: C, 69·0; H, 4·3. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and (ii) from 5-nitro-2-*p*-tolyloxybenzophenone. It formed pale yellow needles, m. p. 150°, from ethanol (Found: C, 68·8; H, 4·2. $C_{20}H_{15}O_4N$ requires C, 68·8; H, 4·3%), and yielded *5-nitro-2-(2-methoxy-4-methylphenoxy)benzophenone* (XIa) as colourless needles, m. p. 100—101° (from methanol) (Found: C, 69·8; H, 4·8. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7%), when methylated either with diazomethane in ether or with methyl sulphate in aqueous sodium hydroxide. By acidifying solutions of (XI) in aqueous or ethanolic potassium hydroxide, which had been kept at room temperature for periods up to 5 days, the compound was recovered mainly unchanged, although the m. p. and mixed m. p. 145—148° was invariably lower even after crystallisation.

5-Nitro-2-(2-hydroxy-5-methylphenoxy)benzophenone (X), m. p. 158° (Found: C, 68·9; H, 4·1. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and *5-nitro-2-(2-hydroxy-6-methylphenoxy)benzophenone*, m. p. 127—128° (Found: C, 68·7; H, 4·4%), were similarly prepared from the appropriate 5-nitro-2-aryloxybenzophenones. When solutions of (X) in acetone and diazomethane in ether were mixed and kept at room temperature for 2 days, concentration of the resulting solution afforded 5-nitro-2-(2-methoxy-5-methylphenoxy)benzophenone (Xa), m. p. and mixed m. p. 120° (from ethanol), whereas methylation of (X) with methyl sulphate in dilute sodium hydroxide gave (XIa), m. p. and mixed m. p. 100—101°. Acidification of a solution of (X) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 24 hours, gave a phenolic product, m. p. 145—147° (from ethanol), unchanged by admixture with (XI) but depressed to m. p. 130—134° by admixture with (X).

5-Nitro-2-(4-nitro-2-hydroxyphenoxy)benzophenone.—A solution of 2 : 7-dinitro-9-phenylxanth-hydrol (0·7 g.) in concentrated sulphuric acid (3 c.c.) was treated successively with acetic acid (6 c.c.) and 30% hydrogen peroxide (1·5 c.c.) and the whole was kept at 40° for 1 hour. After addition to water the solid was collected and extracted with 90% ethanol, leaving an unidentified insoluble residue, m. p. 265° (Found: C, 63·5; H, 3·0%). On cooling (charcoal), the solution deposited colourless needles, m. p. 168—170° when determined in quartz or Jena-glass capillary tubes, but sintering at 166° and melting at *ca.* 200° in tubes of soft glass (Found: C, 60·2; H, 3·3. $C_{19}H_{12}O_7N_2$ requires C, 60·0; H, 3·2%). The *compound* was readily soluble in dilute alkali, acidification yielding a solid, which formed long colourless needles, m. p. 208—210° (quartz), from ethanol (Found: C, 60·1; H, 3·1%). The change in m. p. is probably due to rearrangement to 5-nitro-2-(5-nitro-2-hydroxyphenoxy)benzophenone but attempts to confirm this by methylation with diazomethane gave in each case a gummy product which resisted crystallisation.

3′-5-Dinitro-2-(2-hydroxy-4-methylphenoxy)benzophenone, m. p. 203° (from acetic acid) (Found: C, 61·0; H, 3·5. $C_{20}H_{14}O_7N_2$ requires C, 60·9; H, 3·35%), and *3′-5-dinitro-2-(2-hydroxy-5-methylphenoxy)benzophenone*, m. p. 162° (from methanol) (Found: C, 61·1; H, 3·5%), were prepared in the usual way from 5-nitro-2-*p*- and -*m*-tolyloxybenzophenone respectively (0·5 g.) in concentrated sulphuric acid (2 c.c.) and acetic acid (5 c.c.) by warming with 30% hydrogen peroxide at 40°. The latter product was converted into the former, m. p. and mixed m. p. 201—202°, by dissolution in, and recovery from, dilute potassium hydroxide.

Scissions with Piperidine.—(i) A solution of 5-nitro-2-*o*-hydroxyphenoxybenzophenone (V) in piperidine was heated under reflux for 1 hour. After cooling and addition of benzene, the resulting solution was washed with dilute sulphuric acid and then with dilute sodium hydroxide. Acidification of the alkaline extract and recovery in ether afforded catechol, m. p. and mixed m. p. 103—104°, after distillation (diacetate, m. p. and mixed m. p. 63°). Concentration of the dried benzene solution gave *5-nitro-2-piperidinobenzophenone* (VI), m. p. 100° (from ethanol), identical with a specimen prepared from (I) and piperidine (Found: N, 9·2. $C_{18}H_{18}O_3N_2$ requires N, 9·0%).

(ii) 5-Nitro-2-(2-hydroxy-4-methylphenoxy)benzophenone (XI) when similarly treated with piperidine afforded (VI) and 3 : 4-dihydroxytoluene. The latter was obtained as a red oil after acidification of the alkaline extract and recovery from ether; it afforded a solid distillate, m. p. 64°, and with bromine in acetic acid gave the tribromo-derivative, m. p. 158—160° (Ono and Imoto, *Bull. Soc. Chem. Japan*, 1936, **11**, 127, give m. p. 158°).

(iii) 5-Nitro-2-(2-methoxy-4-methylphenoxy)benzophenone (XIa) likewise yielded (VI) and 4-hydroxy-3-methoxytoluene. The latter was obtained as a pale yellow oil of characteristic odour and giving with ferric chloride in ethanol the blue and green colour reactions mentioned by de Vries (*Rec. Trav. chim.*, 1909, **28**, 276); with picric acid in ethanol it afforded orange-red needles of the picrate, m. p. 98—99° (from aqueous ethanol) (Beilstein records m. p.s 96°, 96·8°, and 112°).

Micro-analyses were carried out by Mr. J. M. L. Cameron.

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14. *The Role of* E_g^+ *Vibrations in the* 2600-A. *Benzene Band System.*

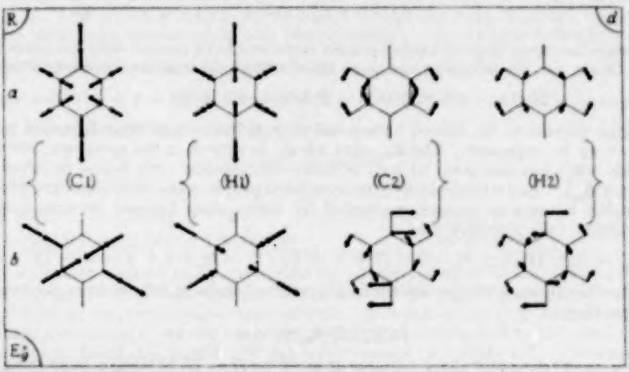
By D. P. Craig.

The observation by Garforth and Ingold (*J.*, 1948, 417) that the two E_g^+(C) vibrations differ strongly in their power to perturb the forbidden $A_{1g} - B_{2u}$ transition in benzene receives an explanation in terms of an assumed mechanism for the perturbation of electronic states by atomic vibrations. The mechanism, which in spite of a certain reasonableness must at present be treated as heuristic, is that each C atom in the benzene ring acts towards non-neighbours as a small positive charge but is completely screened from its neighbours. Electronic wave functions are approximated in terms of structures, and of these the polar ones here play the central part. The energy matrix components are changed in the course of vibrations by electrostatic action between the small charges already mentioned and the unit charges of polar structures. The 606-cm.$^{-1}$ vibration can then be calculated to be more effective, by a factor greater than 100 times, than the 1596-cm.$^{-1}$ vibration in causing the appearance of the forbidden transition. This agrees with the experimental finding.

Herzberg and Teller (*Z. physikal. Chem.*, 1933, *B*, **21**, 410) established the principles, so far as the demands of symmetry are concerned, which govern the disturbances caused to electronic states by atomic vibrations in polyatomic molecules. A spectral transition forbidden by electronic selection rules is made allowed if the symmetry properties of the atomic vibrations change during the transition by a component $\Gamma_{vib.}$ such that

$$\Gamma_{Gd} \times \Gamma_{Exc.} \times \Gamma_{vib.} \subset \Gamma_x, \Gamma_y, \text{ or } \Gamma_z$$

where Γ_{Gd} and $\Gamma_{Exc.}$ are the representations to which the ground and the excited electronic wave functions belong and Γ_x, for example, that of the x vector. However, Garforth and Ingold (*J.*, 1948, 417) showed that, of the four E_g^+ vibrations of benzene capable in principle of making the 2600 A. transition appear, only two actually do so and in these two the motions of the C skeleton are geometrically similar. The figure is part of a block of illustrations used by



E_g^+ Vibration forms of benzene.

Bailey, Ingold, Poole, and Wilson (*J.*, 1946, 222) to show the vibration forms of benzene and it is reproduced here with their permission. It depicts a set of basic E_g^+ motions from which, by linear combination, all possible E_g^+ motions of benzene can be set up. Garforth and Ingold (*loc. cit.*) find that the two vibrations with a large component of either the C1 or the H1 motion—in which, that is, the C hexagon is distorted principally by angle bending and not by bond stretching—are effective, whereas those with a large component of C2 or H2 are ineffective. The latter equally with the former satisfy the symmetry demands but fail to appear on account of some more subtle detail of the atomic motions. To understand how this can happen a mechanism has to be assumed by which the electronic energy comes to depend on the nuclear motion, and this should make it plain how the observed differences come about. A very simple

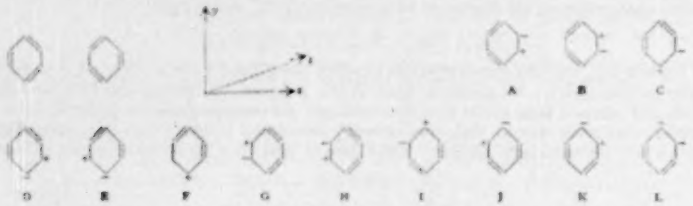
mechanism is applied in this paper to study those two vibrational motions, compounded from C1 and C2, in which the carbon atoms have large amplitudes, and it is found that one of these could be very much more effective than the other in this phenomenon. The effective one is the predominantly bending motion, as required by experiment.

The intense absorption band of benzene at 1700 A. records an $\mathbf{A}_{1g} - \mathbf{E}_u^-$ transition, and any forbidden transition which appears at longer wave-lengths does so mainly by borrowing intensity from this strong band. We concentrate therefore on finding to what extent E_g^+ vibrations cause mixing of the final $\mathbf{B}_{2u}$ state of the forbidden transition with the final $\mathbf{E}_u^-$ state of the allowed one. The coefficient for this mixing is, in perturbation theory,

$$\frac{\int \psi(\mathbf{B}_{2u})(EH_g^+)\psi(\mathbf{E}_u^-)d\tau}{E(\mathbf{B}_{2u}) - E(\mathbf{E}_u^-)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which ψ and E respectively denote unperturbed wave functions and energies, and $H(E_g^+)$ is the perturbing potential of a hexagon distorted in an E_g^+ vibration. The intensity of the transition ending at the $\mathbf{B}_{2u}$ state will bear the same ratio to the allowed $\mathbf{A}_{1g} - \mathbf{E}_u^-$ intensity as the square of the expression (1) bears to unity; hence to compare the perturbing powers of the two E_g^+ vibrations (*i.e.*, the two C vibrations) we have to compare the squares of (1) evaluated for them.

We may write approximate forms for $\psi(\mathbf{E}_u^-)$ and $\psi(\mathbf{B}_{2u})$ in terms of the following structures:



Two $\mathbf{E}_u^-$ wave functions may be made up from these and both involve only the polar structures A to L. Of the two the following one alone may be the final state for intense transitions:

$$\psi(\mathbf{E}_u^-) = (1/\sqrt{24})(2A - 2B + C - D - E + F - 2G + 2H - I + J + K - L) \quad . \quad (2)$$

A degenerate partner to (2), chosen orthogonal to it, is inactive in the mechanism we consider and hence may be neglected. The $\mathbf{B}_{2u}$ state which, to appear in the spectrum, has to become mixed with $\psi(\mathbf{E}_u^-)$ has non-polar as well as polar components. We follow in detail only the polar part, $\psi(\mathbf{B}_{2u})$. The contribution by the non-polar part is in the same sense and proportional, but is smaller because it appears multiplied by the overlap integral between neighbouring atomic orbitals. We therefore take

$$\psi(\mathbf{B}_{2u}) = (1/\sqrt{12})(A + B - C - D + E + F - G - H + I + J - K - L) \quad . \quad . \quad (3)$$

If H be the Hamiltonian for the undistorted hexagonal shape it follows from the symmetry of the problem that

$$\int \psi(\mathbf{E}_u^-) H \psi(\mathbf{B}_{2u}) d\tau = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

A distortion from hexagonal shape replaces H in (4) by $H + H$, H being a perturbing potential having the symmetry of the distortion. When H transforms like E_g^+ the matrix component analogous to that in (4) has a part which transforms like A_{1g} and is not therefore necessarily zero. Small terms being neglected, the totally symmetrical part is

$$\begin{aligned} \int \psi(\mathbf{E}_u^-) H \psi(\mathbf{B}_{2u}) d\tau &= (1/12\sqrt{2})\{2(AHA) - 2(BHB) - (CHC) + (DHD) \ldots \text{etc}\} \\ &= (1/2\sqrt{2})\{(AHA) - (BHB)\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5) \end{aligned}$$

where $(AHA) = \int AHA d\tau$

the second line following from the first because H transforms like E_g^+. The value of this expression, put in (1), determines the intensity of the forbidden band system. Evidently its value depends on the development of energy differences under the perturbing vibration between structures in pairs like A and B which have opposite charge displacements. We therefore

have to investigate the right-hand side of (5) by seeing how the energies of oppositely charged structures are split by atomic motions of specified types.

The energies of these polar structures change during the course of vibrations because the internuclear distances change, and this alters the mutual energy of the charged atoms and the other nuclei. Since at distances greater than a bond length the field of an atom is dominantly electrostatic (the exchange terms being negligibly small) the energy changes we wish to study may be taken to arise from the electrostatic action between the unit positive and negative charges in the structure, and the field of the incompletely screened nuclear charge of the other atoms. Now screening is most complete in the directions of maximum electron density (*i.e.*, bond directions) so it is evident from the outset that a distinction must be made between neighbour and non-neighbour interactions, the former being smaller than the latter by virtue of the more complete screening along the line of the σ bonds. Accordingly we propose, as the simplest reasonable model, that any nucleus acts toward a non-neighbour as a small positive charge $q\mathbf{e}$, but is completely shielded from its immediate neighbours by the bonding electrons. Interest throughout centres on energy differences developed between oppositely charged structures, so that no attention need be paid to the interaction between the charged atoms which changes by the same amount in the two structures. We thus suppose that in any structure there are on the non-charged atoms small residual charges $q\mathbf{e}$, and that energy changes in distorted molecules are a consequence of interactions between the two charged atoms and these small charges on non-neighbours.

We now proceed with the calculation of the perturbation energies. Since the displacements are small compared with a bond length we use the differential expression for change in electrostatic energy :

$$\delta E = (q\mathbf{e}^2/r^2)\delta r = c\mathcal{A}(r_0^2/r^2)\delta r, \text{ where } c\mathcal{A} = q\mathbf{e}^2/r_0^2 \text{ and } r_0 = 1{\cdot}40 \text{ A.}$$

Since $\psi(\mathbf{B}_{2u})$ is symmetric, but $\psi(\mathbf{E}_u^-)$ antisymmetric, to rotation about the x axis, antisymmetry in the vibrational motion will be necessary to cause mixing. Only the lower forms of C1 and C2 need therefore be studied. We suppose the atoms in the lower form of C1 to be displaced a distance $\delta r/2$, and in the lower form of C2 the clockwise displacements are δr and the anticlockwise ones $\delta r/2$. This choice is merely a convenient one for the next step, and the composite motions have later to be normalised to unit kinetic energy. The distortion energies are :

Structure A, distorted according to C1 (lower form)

$$\Sigma\delta E = -2c\mathcal{A}(1/4 + \sqrt{3}/12)\delta r$$

Structure A, distorted according to C2 (lower form)

$$\Sigma\delta E = \tfrac{1}{2}c\mathcal{A}\delta r$$

Substituting in (5), we have

$$\left.\begin{aligned} \int \psi(\mathbf{B}_{2u})H(\mathrm{C1})\psi(\mathbf{E}_u^-)\mathrm{d}\tau &= -\sqrt{2}(1/4 + \sqrt{3}/12)\, c\mathcal{A}\delta r = -0{\cdot}558\, c\mathcal{A}\delta r \\ \int \psi(\mathbf{B}_{2u})H(\mathrm{C2})\psi(\mathbf{E}_u^-)\mathrm{d}\tau &= 1/2\sqrt{2}c\mathcal{A}\delta r \qquad\qquad = 0{\cdot}354\, c\mathcal{A}\delta r, \end{aligned}\right\} \quad . \quad . \quad . \quad (6)$$

The actual molecular motions in E_1^+ vibrations are combinations of C1 and C2 in proportions determined by the force system opposing distortions of the equilibrium hexagon. To find these actual motions we proceed in the simplest way, by supposing the C–H groups concentrated in mass points and taking a valence-force field with C–C stretching and C–C–C planar bending force constants as found by Ingold and his collaborators (*J.*, 1948, 491). Referred to the lower forms of the illustrated motions, the actual motions after being normalised to equal kinetic energies are :

$$0{\cdot}90\mathrm{C1} - 0{\cdot}25\mathrm{C2} : \text{calc. } 616 \text{ cm.}^{-1} \text{ (exptl. } 606 \text{ cm.}^{-1})$$
$$0{\cdot}44\mathrm{C1} + 0{\cdot}52\mathrm{C2} : \text{calc. } 1657 \text{ cm.}^{-1} \text{ (exptl. } 1596 \text{ cm.}^{-1})$$

Using (6), we now find the matrix components for the mixing of $\mathbf{B}_{2u}$ and $\mathbf{E}_u^-$ states by these two vibrations.

$$606 \text{ cm.}^{-1} : \int \psi(\mathbf{B}_{2u})\{0{\cdot}90H(\mathrm{C1}) - 0{\cdot}25\, H(\mathrm{C2})\}\psi(\mathbf{E}_u^-)\,\mathrm{d}\tau = -0{\cdot}591\, c\mathcal{A}\delta r$$

$$1596 \text{ cm.}^{-1} : \int \psi(\mathbf{B}_{2u})\{0{\cdot}44H(\mathrm{C1}) + 0{\cdot}52H(\mathrm{C2})\}\psi(\mathbf{E}_u^-)\,\mathrm{d}\tau = -0{\cdot}063\, c\mathcal{A}\delta r$$

The relative effectiveness of the vibrations per unit excursion of the nuclei is the ratio of the squares of these quantities. Since the low-frequency motion has a larger amplitude than the high, the ratio of squares has to be increased in favour of the 606-cm.$^{-1}$ vibration by a factor (1596/606), making the final result:

$$\frac{\text{Intensity in } \mathbf{A}_{1g} - \mathbf{B}_{2u} \text{ due to 606 cm.}^{-1}}{\text{Intensity in } \mathbf{A}_{1g} - \mathbf{B}_{2u} \text{ due to 1596 cm.}^{-1}} = \frac{(-0{\cdot}591)^2}{(-0{\cdot}063)^2} \times \frac{1596}{606} = 230 : 1$$

We do not wish to insist on the numerical magnitude of the ratio, which is rather sensitive to the elastic constants chosen to determine the motions. However, in making the forbidden transition allowed, the 606-cm.$^{-1}$ vibration is certainly more effective, by a factor greater than 100 times, than the 1596 cm.$^{-1}$, and this agrees with the observation by Garforth and Ingold (*loc. cit.*) that the latter vibration is actually inactive, or very weak, in the spectrum.

An estimate of the intensity $\mathbf{A}_{1g} - \mathbf{B}_{2u}$. With one further assumption it is possible to form an estimate of the stolen intensity in the 2600-A. band system. Such a calculation, compared with experiment, gives a partial check of the mechanism of perturbation that has been assumed. The quantity required for evaluating (1) is $q\boldsymbol{e}$, from which $\mathscr{A}$ can be found. For this we use Slater's rules for atomic screening constants, and suppose that at remote points a nucleus has the field expected outside the atomic configuration $(1s)^2(2s, 2p)^4$. This gives $q\boldsymbol{e} = -0{\cdot}6$ electron. The root mean square excursion of a nucleus in the 606-cm.$^{-1}$ vibration is 0·064 A., and the coefficient of $\phi(\mathbf{B}_{2u})$ in the full wave function for the $\mathbf{B}_{2u}$ state (including non-polar as well as polar structures) is about 0·5. The perturbation matrix component is

$$\int \phi(\mathbf{B}_{1g}) H \phi(\mathbf{E}_u^-) d\tau = 0{\cdot}09 \; e\text{V}.$$

and this, through (1), gives f (calc.) = 0·0014 as the calculated stolen intensity. The experimental value is f (exptl.) = 0·002. The close agreement is fortuitous. The important thing is the agreement in order of magnitude and the calculation is satisfactory to that extent.

I am very much indebted to Prof. C. K. Ingold, F.R.S., and to Dr. Edward Teller, for discussions on this subject. I also thank Prof. Ingold and his collaborators for permission to reproduce their diagram of vibration forms. The work described has been carried out during the tenure of a Turner and Newall Fellowship in the University of London.

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University College, London. [*Received, September 26th*, 1949.]

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15. *Preparation of* L-*Threonine. Interconversion of the Four Stereoisomeric* α-*Amino-*β-*hydroxybutyric Acids.*

By D. F. Elliott.

Resolution of *trans*-DL-5-phenyl-5-methyl-Δ^4-oxazoline-4-carboxylic acid with brucine affords the L-form (I) of the acid as a crystalline brucine salt. The D-form (IV) remaining in the mother-liquors was also converted into (I) by a stepwise inversion process. Almost all of the racemic acid was thus transformed into the L-form. Hydrolysis of (I) gave pure L-threonine in 22% overall yield from hippuric acid. A cycle of asymmetric transformations has been worked out whereby any one of the four stereoisomers of α-amino-β-hydroxybutyric acid may be prepared from (I). The configurations of the two *allo*threonines have been determined by reference to L-threonine.

In a previous paper (Elliott, *J.*, 1949, 589) it was shown that both stereoisomeric DL-forms of ethyl 2-phenyl-5-methyl-Δ^4-oxazoline-4-carboxylate gave, on hydrolysis with aqueous alkali, the *trans*-acid which is configurationally related to threonine. As a result of this discovery the overall yield of DL-threonine obtained in the synthesis from hippuric acid (Attenburrow, Elliott, and Penny, *J.*, 1948, 310) was considerably increased. It was apparent from the data accumulated in this work that it should be possible to evolve a cycle of asymmetric transformations for the interconversion of the four stereoisomers of α-amino-β-hydroxybutyric acid (cf. Elliott, *Nature*, 1948, **162**, 657). The conversion of D-threonine into its optical antipode was particularly desirable. Realisation of these possibilities depended on the asymmetry of the molecule being retained during the cyclisation of ethyl α-benzamido-β-hydroxybutyrate with thionyl chloride which was described in a previous paper (Elliott, 1949, *loc. cit.*). Owing to the presence of two asymmetric centres it was not possible to obtain unequivocal evidence on this point by working with the racemic substances. It could always be argued that the inversion

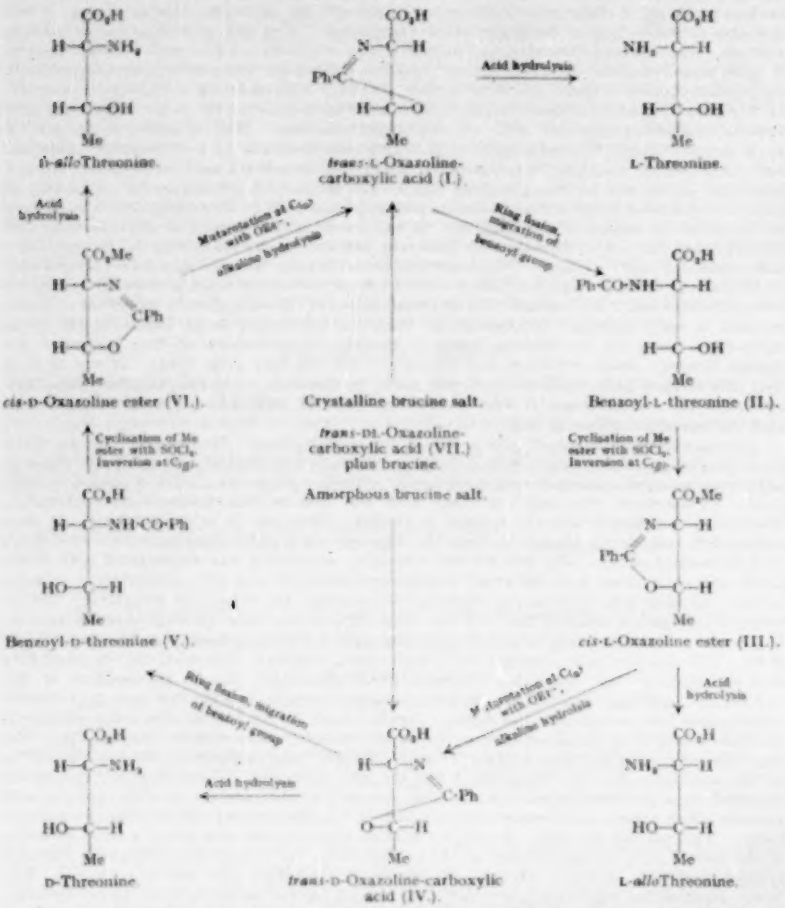
took place through an optically inactive intermediate by destruction, followed by regeneration, of both centres of asymmetry.

Resolution of DL-*N*-formyl-*O*-methylthreonine has been described by West and Carter (*J. Biol. Chem.*, 1937, **119**, 109); this compound is not easily accessible from threonine itself, but only from crotonic acid. The main aim of the present investigation being to find a convenient synthesis of L-threonine from hippuric acid with the minimum number of steps it was desirable to resolve one of the intermediate compounds. This task proved to be exceedingly difficult. DL-*N*-Benzoylthreonine received a great deal of attention with complete lack of success. It gave non-crystalline salts with brucine, quinine, cinchonine, and ϕ-ephedrine, whereas with 1-phenylethylamine it gave sparingly soluble diastereo-compounds in a variety of solvents. DL-N-*Formyl-O-benzoylthreonine* prepared from DL-*O*-benzoylthreonine in the usual way also gave a diastereo-compound with (−)-1-phenylethylamine. Mild alkaline hydrolysis of DL-*N*-formyl-*O*-benzoylthreonine gave DL-N-*formylthreonine* which was a very soluble compound and could not be resolved. Various other derivatives were tried without success. At this point the choice was becoming limited and it was decided to investigate the resolution of *trans*-DL-2-phenyl-5-methyl-Δ^3-oxazoline-4-carboxylic acid (VII). This compound was the last to be considered because of its instability; it was known to be sensitive to dilute mineral acid (Elliott, 1949, *loc. cit.*). Considerable time was devoted to the resolution of the oxazoline-carboxylic acid with (+)- and (−)-1-phenylethylamine because it would then have been possible to obtain both forms in a state of purity. Although partial success was achieved this resolution was abandoned when it was found that recrystallisation of the salts, even in anhydous solvents, resulted in fairly extensive decomposition. This was attributed to an attack on the cyclic imino-ether group by the primary amine to produce an open-chain amidine derivative (cf. Barber, Gregory, Slack, Stickings, and Woolman, *CPS*, 66, May 24th, 1944). It was obvious that only tertiary bases could be used with safety in this case. (−)-Ethyl-1-phenyldimethylamine (Snyder and Brewster, *J. Amer. Chem. Soc.*, 1949, **71**, 291) did not give a crystalline salt with the oxazoline-carboxylic acid.

Success was finally achieved with brucine as the resolving base. Fortunately only one of the diastereoisomeric salts crystallised and this was extremely well defined. It was quite stable in anhydrous solvents, possessed very satisfactory solubility properties, and was formed in high yield. Furthermore, the acid combined with the brucine was trans-L-*2-phenyl-5-methyl-*Δ^3*-oxazoline-4-carboxylic acid* (I), because it yielded L-threonine on acid hydrolysis. It then remained to test out the ideas concerning the interconversion of the stereoisomeric forms which were mentioned above. The brucine salt remaining in solution was decomposed with dilute alkali and chloroform, and the crude D-oxazolinecarboxylic acid (IV) converted in solution without isolation into *N*-benzoyl-D-threonine (V) through the *O*-benzoyl derivative. Polarimetric investigation revealed that not less than 70% of the crude product was the D-form. The benzoyl compound was esterified with diazomethane and cyclised with thionyl chloride at 0°. The oxazoline ester obtained had a high optical rotation; this ruled out the possibility that the crotonic acid derivative, $CHMe{:}C(NH{\cdot}CO{\cdot}Ph){\cdot}CO_2Me$ was an intermediate in the cyclisation. Although this had always been considered remote, it is the first time that definite evidence has been obtained on this point. Previous work has shown that the action of thionyl chloride on ethyl α-benzamido-β-hydroxybutyrate causes cyclisation with inversion at C_β. The oxazoline ester obtained from impure (V) must therefore have consisted of not less than 70% of the *cis*-D-form (VI), the remainder being the *cis*-L-form (III). According to experiments described in a previous paper (Elliott, 1949, *loc. cit.*) mild hydrolysis of this mixture with aqueous alkali should have caused mutarotation at $C_{(\alpha)}$, thus giving the corresponding *trans*-forms. This was not the case. A complex mixture resulted from which only a small quantity of the *trans*-L-form (I) was isolated as the brucine salt. DL-*N*-Benzoyl*allo*threonine was also isolated from this mixture. Clearly, incomplete mutarotation had occurred at $C_{(\alpha)}$. The earlier experiments referred to above had been carried out on the ethyl *cis*-DL-oxazoline ester, mutarotation appearing to be complete. Failure to obtain the same results with the corresponding optically active methyl ester was attributed to the much faster rate of hydrolysis of this compound. It seemed probable that mutarotation ceased as soon as the ester group had been removed.

In order to gain further information concerning the rate of this mutarotation under various conditions, experiments were conducted on *methyl* cis-L-*2-phenyl-5-methyl-*Δ^3*-oxazoline-4-carboxylate* (III) which was readily obtainable in pure form. Pure benzoyl-L-threonine (II) was prepared from the brucine salt of (I) and was esterified with diazomethane. The *benzoyl-L-threonine methyl* ester was cyclised with thionyl chloride to give the pure oxazoline ester

(III) in good yield. Mutarotation studies on this compound were carried out polarimetrically. In a mixture of equal parts of N-sodium hydroxide and alcohol mutarotation occurred to a much greater extent than with aqueous alkali, but conversion into (IV) was still not complete. This was the case even when the alkali was present in excess, showing that the free acid corresponding



In this scheme the prefixes D- or L- refer to the configuration at $C_{(\alpha)}$, as in all amino-acids, but the projection formulæ are those conventionally used for carbohydrates.

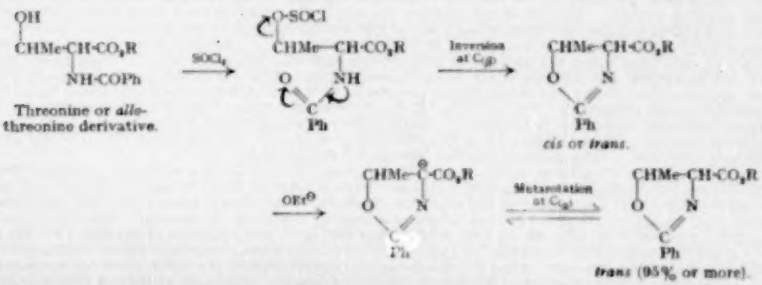
to (III) did not undergo mutarotation. In alcoholic sodium ethoxide solution at room temperature mutarotation was immeasurably fast; after addition of water to the solution, followed by short refluxing to hydrolyse the ester group, the rotation of the solution revealed that about 95% conversion into the *trans*-D form (IV) had occurred.

Application of these experimental conditions to the impure *cis*-D-oxazoline ester (VI), obtained from the amorphous brucine salt as described above, gave the desired result. The

yield of (I) isolated as the brucine salt from the product was approximately that expected from the specific rotation of the crude benzoyl-D-threonine. The total yield of brucine salt obtained from the resolution of the oxazoline-carboxylic acid and from the inversion of the D-form was about 75% (based on the utilisation of both forms) of slightly impure material. It was recrystallised twice with a loss of 10—15%. The overall yield of L-threonine from hippuric acid was 22%; this could have been raised by re-utilisation of the mother-liquors, but for ordinary preparative work this seemed hardly necessary. Recently, Pfister, Robinson, Shabica, and Tishler (*J. Amer. Chem. Soc.*, **1949**, **71**, 1101) have described a synthesis of DL-threonine in good overall yield from acetoacetic ester, and in a later paper from the same laboratories (Zambito, Peretz, and Howe, *ibid.*, p. 2541) resolution through the *p*-nitrobenzoyl derivative is reported. Although it was known that the resolution of DL-*p*-nitrobenzoylserine had been accomplished by Fischer and Jacobs (*Ber.*, 1906, **39**, 2942) this method of resolving DL-threonine was not investigated in this laboratory because it would have added extra stages to the synthesis. Fortunately, the present investigation was greatly simplified by the successful resolution of the oxazoline-carboxylic acid, which lies directly on the synthetic pathway from hippuric acid. It must be admitted that the oxazoline-carboxylic acid is not an ideal substance for resolution because of its instability, but by careful attention to experimental detail this disadvantage can be overcome.

The *trans*-L-oxazoline-carboxylic acid (I), which can be obtained absolutely pure as the brucine salt, is the key substance from which all four stereoisomers of α-amino-β-hydroxybutyric acid were prepared as shown in the reaction scheme. The yields were good at every stage. It has been shown (Elliott, 1949, *loc. cit.*) that the ethyl ester hydrochlorides of threonine or *allo*threonine are converted into the corresponding oxazoline esters with retention of configuration at both asymmetric centres on treatment with benzimino ethyl ether. Thus it is possible to leave and re-enter the main pathway (I to VI) at will; all four stereoisomers are therefore easily interconvertible. This cycle of interconversions establishes the configurations of the *allo*threonines relative to L-threonine. L-*allo*Threonine was dextrorotatory in water and much more so in N-HCl. This increase in positive rotation on conversion into the cation is in agreement with Clough's rule concerning naturally occurring amino-acids (Clough, *J.*, 1915, **107**, 1509; 1918, **113**, 526). The preparation of D- and L-*allo*threonine was first carried out by West and Carter (*J. Biol. Chem.*, 1938, **122**, 611). The specific rotations of these substances prepared by the present method are in good agreement with those recorded by West and Carter.

The asymmetric transformations described in this paper can be explained satisfactorily by the reaction mechanisms previously proposed by the author which are summarised below:



The term mutarotation has been applied to the inversion of configuration which occurs when the *cis*-oxazoline esters are brought into contact with ethoxide ions. It is believed that this expression correctly describes the phenomenon, because the final product is probably an equilibrium mixture containing a small but definite amount of the *cis*-isomer. The evidence from the polarimetric study is that at least 95% of the *trans*-form was present after equilibration and hydrolysis. No figures were available for the rotation of the corresponding *cis*-oxazoline-carboxylic acid, but as judged by the figures for the rotation of the methyl esters the sign would have been opposite to that for the *trans*-form. The fact that the optical rotation did not reach the theoretical figure after equilibration could be explained by decomposition to optically

inactive substances, or to the presence of a very small quantity of the *cis*-form. The remarkable stereochemical specificity of this reaction must be attributed to powerful steric forces.

Experimental.

(M. p.s are uncorrected.)

DL-*N-Formyl-O-benzoylthreonine*.—Ethyl DL-*trans*-2-phenyl-5-methyl-Δ^4-oxazoline-4-carboxylate (2·3 g.) was refluxed with 0·5*N*-sodium hydroxide (22 ml.) until dissolved, and then cooled to room temperature, and 5*N*-hydrochloric acid (4·2 ml., 2 equivs.) was added. After 4 hours hydrated sodium acetate (1·4 g.) was added with stirring. The main bulk of the *O*-benzoylthreonine separated rapidly. It was filtered off; the mother-liquors were evaporated to obtain a second crop and were finally evaporated to dryness under reduced pressure. The solids were combined, mixed with 90% formic acid (10 ml.), and warmed to 45°, and acetic anhydride (3 ml.) was added dropwise with shaking. The solution was then heated to 80° for 15 minutes and evaporated to dryness under reduced pressure. The residue was lixiviated with cold water to remove sodium chloride and dried at 100°. DL-*N-Formyl-O-benzoylthreonine* (1·9 g., 76%) formed irregular masses of prisms (from hot water), m. p. 172—173° (Found: C, 57·2; H, 5·25; N, 5·45. $C_{12}H_{13}O_4N$ requires C, 57·4; H, 5·2; N, 5·6%).

The salt with (+)-1-phenylethylamine had m. p. 154—155°. The *N*-formyl-*O*-benzoylthreonine liberated on addition of acid to an aqueous solution of this salt was optically inactive.

DL-*N-Formylthreonine*.—The corresponding *O*-benzoyl compound (1·9 g.) was suspended in water (10 ml.), and 5*N*-sodium hydroxide added dropwise until the acid was neutralised. An additional 1·65 ml. of 5*N*-sodium hydroxide was then added and the solution set aside 30 minutes at room temperature. The solution was then treated with 5*N*-hydrochloric acid (3·1 ml.), the benzoic acid was filtered off, and the filtrate extracted thoroughly with light petroleum. The aqueous layer was evaporated to dryness under reduced pressure, the residue was extracted with warm ethanol (20 ml.) and filtered from sodium chloride, and the filtrate again evaporated to dryness. The residue was dissolved in dry dioxan, a small amount of resinous material was filtered off, and the solvent removed under reduced pressure. The residual oil was dissolved in a small quantity of anhydrous ethanol, and anhydrous ether was added until a cloudiness was produced. On storage at 0° DL-*N-formylthreonine* (0·4 g., 36%) separated in heavy prisms, m. p. 104°. It was recrystallised from ethanol–ether and then had m. p. 105—106°, which changed to 125—126° during storage for several weeks in a closed tube (Found: C, 41·0; H, 6·7; N, 9·3. $C_5H_9O_4N$ requires C, 40·8; H, 6·2; N, 9·5%). Owing to the unsatisfactory yield of this substance, attempts at resolution were abandoned after a few unsuccessful experiments.

DL-*trans*-2-*Phenyl-5-methyl-*Δ^4-*oxazoline-4-carboxylic Acid* (VII).—This compound may be prepared from the corresponding pure ethyl *trans*-oxazoline ester (obtained from DL-threonine ethyl ester hydrochloride and benzimino ethyl ether), in which case the yield was 87%, or from the mixture of *cis*- and *trans*-oxazoline esters obtained in the synthesis of DL-threonine from hippuric acid, as follows. The mixture of esters obtained as described by Elliott (1949, *loc. cit.*) was distilled and the fraction of b. p. 110—130°/0·05 mm. collected. The yield of purified product was 75% calculated on crude ethyl α-benzamido-β-hydroxybutyrate. The ester mixture (46·6 g.) was added to *N*-sodium hydroxide (220 ml.); after addition of ethanol (220 ml.) the solution was refluxed for 15 minutes and then evaporated to 150—200 ml. under reduced pressure. The solution was cooled to 0° in an alcohol–solid carbon dioxide bath and efficiently stirred whilst 5*N*-hydrochloric acid (*ca.* 44 ml.) was added dropwise, the temperature being maintained at 0° throughout; the addition of the acid required 20—30 minutes. Local excess of acid was carefully avoided. The pH of the solution was tested from time to time by means of Johnson's universal indicator paper, and when it had fallen to 3·5—4·0 the addition of acid was stopped. Generally, about 90% of the theoretical amount of acid was required. The oxazolinecarboxylic acid usually began to crystallise before the addition of hydrochloric acid was complete; when it was delayed, the solution was seeded and the sides of the vessel were scratched. After the addition of hydrochloric acid was complete the solution was stirred for 15 minutes at 0° with occasional scratching of the vessel to complete the crystallisation. The acid was filtered by suction, washed with a small quantity of ice-water, and dried as quickly as possible over sodium hydroxide and concentrated sulphuric acid in an efficient vacuum. The acid appeared to be quite stable when dry. The yield was 28·5 g. (71%) and the m. p. 134—137°. This material was pure enough for further work.

trans-L-2-*Phenyl-5-methyl-*Δ^4-*oxazoline-4-carboxylic Acid* (I).—(a) *Resolution of the* DL-*acid*. The acid (28·4 g.) was added to a solution of anhydrous brucine (54·5 g.) in dry ethanol (110 ml.), and the mixture heated until all or most of the solid had dissolved. Anhydrous ethyl acetate (250 ml.; distilled over phosphoric oxide) was then added and heating continued if necessary. After a further addition of dry ethyl acetate (300 ml.) the solution was kept at 0° with exclusion of moisture for 4 days. The crop of crystalline solid was filtered off and washed with a little anhydrous ethyl acetate. The mother-liquors and washings were evaporated to dryness under reduced pressure at a temperature not exceeding 45°. The residue was dissolved in a mixture of anhydrous ethanol (16 ml.) and anhydrous ethyl acetate (80 ml.) and kept at 0° for 3 days. The second crop was treated as before. The total yield of slightly impure brucine salt was 35·6 g. (82%). The m. p. of the salt was variable; melting was generally over a 2° range between the limits 128° and 140°. Crystallisation of the salt from aqueous methanol or ethanol gave a salt, m. p. 162—164°, but some decomposition (of unknown nature) to an oily substance also occurred. Crystallisation of the salt from anhydrous ethanol, on the other hand, gave an excellent recovery of crystalline material. The m. p. was again somewhat variable: in 3 separate experiments, 128°, 131—132°, and 132—133°. It was established that there was no difference in the purity of the three samples, by decomposition, as described below, to L-threonine which in every case had the correct specific rotation. The impure brucine salt (35·6 g.) was crystallised twice from anhydrous ethanol (180 ml. and 160 ml. respectively). The yield of pure salt was 31 g. (70%). Analysis showed that the pure salt contained one molecule of alcohol of crystallisation (Found: C, 66·2; H, 6·7; N, 6·7. $C_{44}H_{54}O_9N_2,C_2H_5OH$ requires C, 67·0; H, 6·7; N, 6·5%). $[\alpha]_D^{20}$ was +13·6° (*c*, 6 in chloroform).

(b) *Inversion of the* D-*isomer.* The mother-liquors from the resolution and from the crystallisation of the salt were combined and evaporated to dryness under reduced pressure below 45°. The residual frothy mass was shaken with N-sodium hydroxide (100 ml.) and chloroform (200 ml.) until completely dissolved. The aqueous layer was extracted twice more with chloroform, the chloroform extracts were combined and washed once with water, and the two aqueous layers combined. To the aqueous solution was then added 5N-hydrochloric acid (*ca.* 38 ml.) with stirring to pH 1 (glass electrode). This caused ring fission of the D-oxazoline-carboxylic acid to D-*O*-benzoylthreonine. After 4 hours at room temperature 5N-sodium hydroxide (*ca.* 36 ml.) was added to the solution with stirring until alkalinity to phenophthalein was attained. The *O*-benzoyl-D-threonine separated as a crystalline solid halfway through the neutralisation and then redissolved. The solution of crude *N*-benzoyl-D-threonine was acidified (Congo-red) with concentrated hydrochloric acid and extracted 6 times with an equal volume of ethyl acetate. The combined ethyl acetate extracts were shaken with a small quantity of anhydrous sodium sulphate, filtered, and evaporated to small bulk under reduced pressure. The benzoyl compound rapidly crystallised. It was filtered off and washed with a little ethyl acetate. The mother-liquors were evaporated to dryness under reduced pressure and kept over concentrated sulphuric acid and sodium hydroxide in a vacuum desiccator until quite solid. The two crops of solid (18 g., 89%) were mixed and ground together in a mortar. $[\alpha]_D^{20}$ was −12·75° (*c*, 1·7 in water).

The solid was suspended in ether (200 ml.) and esterified by careful addition, with shaking, of an ethereal solution of diazomethane in slight excess. On evaporation of the ether the crude methyl ester remained as a syrup which rapidly solidified; it was dried in a vacuum desiccator over concentrated sulphuric acid. The yield was 18·55 g. (97%).

The powdered methyl ester was added in small portions, with stirring, to thionyl chloride (53 ml.; purified by distillation over quinoline and linseed oil) which was cooled to 0—5°. The temperature was not allowed to rise above 5° during the addition. The mixture was allowed to stand overnight at 0°; excess of thionyl chloride was then removed under diminished pressure below 35°. The residue, which frequently crystallised, was dissolved in dry chloroform and without delay the solution was poured slowly into sodium carbonate solution (10%; 250 ml.) with efficient stirring. If necessary, addition of solid sodium carbonate was made to prevent the solution becoming acid. The chloroform layer was separated, the aqueous layer was extracted once more with chloroform, and the combined chloroform extracts were washed with water, dried and distilled. The product (14·3 g., 83·5%) had b. p. 110—115°/0·03 mm., $[\alpha]_D^{20}$ −36·7° (*c*, 4·5 in ethanol). This was a mixture of the two methyl *cis*-oxazoline esters (III) and (VI), containing about 70% of the latter.

The mixture was dissolved in dry ethanol (69 ml.), and to it was added a solution of sodium (1·58 g.; 5% excess over 1 mol.) in dry ethanol (69 ml.). After the solution had been kept for 5 minutes at room temperature, water (138 ml.) was added and the mixture refluxed for 15 minutes. The solution was evaporated under reduced pressure to about 50 ml. and cooled to 0°, and 5N-hydrochloric acid (13·7 ml.; exactly equivalent to the sodium used) added dropwise with stirring, with the precautions referred to above in the isolation of the DL-oxazolinecarboxylic acid from its sodium salt. The product (11·55 g., 86·5%), m. p. 151—154° with previous softening, was a mixture of the *trans*-oxazolinecarboxylic acids (IV) and (I) containing about 70% of the latter. The acid was added to a solution of anhydrous brucine (22·2 g.) in anhydrous ethanol (160 ml.) and heated until dissolved. The crystalline brucine salt (29·1 g., 72% calc. on the methyl oxazoline ester), m. p. 126—128°, separated on cooling. It was recrystallised twice from absolute ethanol (*ca.* 5 parts), giving 24·9 g. of pure salt, m. p. 127—129°.

The total yield of pure brucine salt from (*a*) and (*b*) was 55·9 g. (62·5%, calc. on the oxazoline-carboxylic acid).

The salt (27·4 g.) was decomposed with N-sodium hydroxide (50 ml.) and chloroform in the usual way, and the aqueous layer cooled to 0° and treated with 5N-hydrochloric acid (10 ml.) with the usual precautions. trans-L-2-*Phenyl-5-methyl-*Δ^3-*oxazoline-4-carboxylic acid* separated in small hexagonal plates (7·1 g., 78%), m. p. 162—163°, $[\alpha]_D^{20}$ +109·8° (*c*, 10 in 1 : 1 ethanol–N-aqueous sodium hydroxide), +108·2° (*c*, 6·25 in the same solvent) (Found: N, 6·7. $C_{11}H_{11}O_3N$ requires N, 6·8%).

*N-Benzoyl-*L-*threonine* (II).—The corresponding *trans*-L-oxazoline-carboxylic acid was dissolved in 1 equivalent of N-hydrochloric acid at room temperature, and after 4 hours at room temperature the solution was back-titrated with alkali etc., as described above for the preparation of crude benzoyl-D-threonine. Benzoyl-L-threonine was formed in almost theoretical yield. Recrystallised from ethyl acetate it had m. p. 146—148°, $[\alpha]_D^{20}$ +25·8° (*c*, 1·4 in water). West and Carter (1937, *loc. cit.*) recorded $[\alpha]_D^{20}$ +25·1 (in water). *Benzoyl-*L-*threonine methyl ester*, prepared (93%) in the usual way with diazomethane and crystallised from ether, had m. p. 96°, $[\alpha]_D^{20}$ +23·2° (*c*, 5·4 in ethanol) (Found: N, 6·1. $C_{12}H_{15}O_4N$ requires N, 5·9%).

Methyl cis-L-2-*Phenyl-5-methyl-*Δ^3-*oxazoline-4-carboxylate* (III).—Benzoyl-L-threonine methyl ester (7 g.) was cyclised with thionyl chloride (20 ml.) at 0° as described above for crude benzoyl-D-threonine methyl ester. The yield of *oxazoline* ester, b. p. 110—115°/0·01 mm., was 6 g. (93%). It solidified on storage to a colourless solid which was crystallised from light petroleum (b. p. 40—60°), forming dense prisms, m. p. 74—75°, $[\alpha]_D^{20}$ +69·2° (*c*, 8·5 in ethanol) (Found: N, 6·7. $C_{12}H_{13}O_3N$ requires N, 6·4%).

Polarimetric Investigations of the Mutarotation and Hydrolysis of Methyl cis-L-2-*Phenyl-5-methyl-*Δ^3-*oxazoline-4-carboxylate.*—Aqueous alcoholic sodium hydroxide was prepared by diluting N-sodium hydroxide (50 ml.) to 100 ml. with ethanol. The oxazoline ester (1·095 g., 0·005 mol.) was dissolved in the sodium hydroxide solution (11 ml.). Unfortunately the rotation could not be measured at once because of a cloudiness which developed. After centrifugation in a stoppered tube the solution was placed in a 1-dm. polarimeter tube. Zero time was arbitrarily chosen as the instant when all the oxazoline ester had dissolved in the sodium hydroxide solution. The following readings were obtained at 23° (zero of instrument 360°) (the second place of decimals was not considered significant in this rough experiment):

After 8 mins.	352·2°	After boiling for 2 mins.	352·0°
After 51·5 mins.	352·2	After boiling for 15 mins.	352·0

It was known that hydrolysis of the ester group would certainly be complete after 15 minutes' boiling. The final rotation of the solution should have been −10·2° instead of −8·0° if complete conversion into the *trans*-isomer had occurred. From the very small change in rotation that took place after the first 8 minutes it seemed probable that hydrolysis was complete in this time. To test whether further mutarotation took place after hydrolysis in the presence of excess of alkali, a portion of the above solution was diluted with the 0·5N-aqueous-alcoholic sodium hydroxide and the rotation of the solution measured before and after 15 minutes' boiling. There was no change in the rotation of the solution, which had the expected value when allowance was made for the dilution.

The oxazoline ester (1·095 g.) was dissolved in anhydrous ethanol (10 ml.) containing exactly 1 equivalent of sodium ethoxide. Polarimeter readings were taken in a 1-dm. tube at 24—25°. After 4 minutes from zero time which was arbitrarily chosen as before, the reading was 350·8° and no further change took place on storage for one hour. The ester in solution was hydrolysed by addition of water (10 ml.), followed by boiling for 15 minutes. The rotation of the solution was then −5·0°. For complete conversion into the *trans*-isomer it should have been −5·6°. From the rotation of the methyl *cis*-L-oxazoline ester it seemed probable that the *cis*-L-oxazolinecarboxylic acid would possess a high rotation opposite in sign to that of the *trans*-L-oxazolinecarboxylic acid. On the basis of this assumption the extent of the conversion was approx. 90%.

L-allo*Threonine*.—The methyl *cis*-L-oxazoline ester (2 g.) was refluxed 5 hours with 6N-hydrochloric acid (20 ml.), the solution was cooled, extracted with ether to remove benzoic acid, and evaporated to dryness under reduced pressure. The residual syrup was dissolved in hot ethanol (20 ml.) and excess of pure pyridine added. On cooling L-*allo*threonine separated as dense prisms (1·05 g., 96%). It was recrystallised from 50% aqueous ethanol and had m. p. 273—274° (decomp.), $[\alpha]_D^{20}$ +9·3° (*c*, 3·8 in water), and $[\alpha]_D^{20}$ +32·5° (*c*, 8·2 in N-hydrochloric acid) (Found: N, 11·7. Calc. for $C_4H_9O_3N$: N, 11·8%). West and Carter (1938, *loc. cit.*) recorded $[\alpha]_D^{20}$ +9·6° (in water) for their dextrorotatory isomer.

trans-D-2-*Phenyl-5-methyl-*Δ^1-*oxazoline-4-carboxylic Acid* (IV).—The methyl *cis*-L-oxazoline ester (III) was treated with sodium ethoxide, etc., as described above for the crude D-isomer. The *trans*-D-acid had m. p. 163—164° and $[\alpha]_D^{20}$ −106·1° (*c*, 5·4 in 1 : 1 ethanol–N-aqueous sodium hydroxide).

*N-Benzoyl-*D-*threonine* (V).—The methyl *cis*-L-oxazoline ester (III) (7·9 g.) was treated with sodium ethoxide, etc., as described above except that the oxazoline-carboxylic acid was not isolated but was converted in solution into *N*-benzoyl-D-threonine in the usual way (see above). The product was recrystallised from ethyl acetate. The pure material (6 g., 75%) had m. p. 145—146° and $[\alpha]_D^{20}$ −25·1° (*c*, 1·5 in water) (Found: N, 6·0. Calc. for $C_{11}H_{13}O_4N$: N, 6·3%). West and Carter (1937, *loc. cit.*) recorded $[\alpha]_D^{20}$ −25·5° (in water) for this compound. *Benzoyl-*D-*threonine methyl ester*, prepared with diazomethane in the usual way, had m. p. 96°, $[\alpha]_D^{20}$ −23·3° (*c*, 6 in ethanol) (Found: N, 5·9. $C_{12}H_{15}O_4N$ requires N, 5·9%).

D-*Threonine*.—In this case the amino-acid was prepared from benzoyl-D-threonine and not from (IV) as shown in the chart. The benzoyl compound (2 g.) was hydrolysed as in the preparation of L-*allo*threonine. D-Threonine (yield, 0·95 g., 89%) formed aggregates of hexagonal plates (from 80% ethanol), m. p. 264° (decomp.), $[\alpha]_D^{20}$ +28·4° (*c*, 4·4 in water) (Found: N, 11·5. Calc. for $C_4H_9O_3N$: 11·8%). West and Carter (1937, *loc. cit.*) gave $[\alpha]_D^{20}$ +28·4° (in water).

Methyl cis-D-2-*Phenyl-5-methyl-*Δ^1-*oxazoline-4-carboxylate* (VI).—This *ester* was prepared from benzoyl-D-threonine methyl ester, as described for the L-isomer, in 88% yield. It had m. p. 75—76°, $[\alpha]_D^{20}$ −68·9° (*c*, 8·4 in ethanol) (Found: N, 6·6. $C_{12}H_{13}O_3N$ requires N, 6·4%).

D-allo*Threonine*.—This substance was prepared from (VI) in the usual way, in 94% yield. It had m. p. 272—273° (decomp.), $[\alpha]_D^{20}$ −9·1° (*c*, 3·9 in water) (Found: N, 11·7. Calc. for $C_4H_9O_3N$: N, 11·8%). West and Carter (1938, *loc. cit.*) gave $[\alpha]_D^{20}$ −9·11° (in water).

L-*Threonine*.—The pure brucine salt of the *trans*-L-oxazolinecarboxylic acid (I) (4·09 g.) was decomposed with N-sodium hydroxide (200 ml.) and chloroform in the usual way. To the aqueous layer was then added 10N-hydrochloric acid (440 ml.), the solution was diluted to 700 ml., and the mixture was refluxed for 5 hours. After cooling, benzoic acid was removed by one extraction with ether, and the aqueous layer was evaporated to dryness under diminished pressure. The residue was extracted with hot ethanol (99%; 400 ml.); the solution was filtered from sodium chloride, and pyridine (25 ml.) added to the filtrate. After 24 hours at 0° the L-threonine (1·7 g., 85%; $[\alpha]_D^{20}$ −27·45° (*c*, 2·8 in water)] was collected and washed with absolute alcohol. It was crystallised from 80% ethanol and formed hexagonal plates, m. p. 262—263° (decomp.), $[\alpha]_D^{20}$ −28·3° (*c*, 6 in water), $[\alpha]_D^{20}$ −28·5° (*c*, 2·4 in water) (Found: N, 11·7. Calc. for $C_4H_9O_3N$: N, 11·8%). West and Carter (1937, *loc. cit.*) recorded $[\alpha]_D^{20}$ −28·3° (in water). The yield of pure amino-acid was 1·6 g. (80% calc. on the brucine salt.).

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16. *Acetylene Reactions. Part VI. Trimerisation of Ethynyl Compounds.*

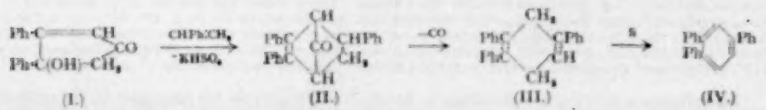
By J. D. Rose and F. S. Statham.

Dicarbonyldi(triphenylphosphino)nickel catalyses the polymerisation of phenylacetylene to the hitherto unknown 1 : 2 : 4-*triphenylbenzene*, the structure of which is demonstrated by unambiguous synthesis. Phenylethynylcarbinol is trimerised to 1 : 3 : 5-*tri*-(α-*hydroxybenzyl*)-*benzene*, which is oxidised to the known 1 : 3 : 5-tribenzoylbenzene.

Information from Germany after the end of the war (cf. F.I.A.T. Final Report No. 933, H.M.S.O., London, 1946) contains references to a catalyst, dicarbonyldi(triphenylphosphino)nickel, of the composition $(Ph_3P)_2Ni(CO)_2$, alleged to be active in the synthesis of acrylic acid derivatives from acetylenes and nickel carbonyl. A sample of this catalyst had been prepared in these laboratories, and on the appearance of the paper by Reppe and Schweckendiek (*Annalen*, 1948, **560**, 104) which contains, *inter alia*, an account of the trimerisation of propargyl alcohol by this catalyst to a mixture of 1 : 2 : 4- and 1 : 3 : 5-tri(hydroxymethyl)benzene, the trimerisation of a series of acetylenic compounds was investigated.

The catalyst is prepared by interaction of triphenylphosphine (2 moles) and nickel carbonyl (1 mole) in ether and separates as a pale cream-coloured crystalline powder which cannot be recrystallised without decomposition. From its solution in cold benzene nickel hydroxide is precipitated within a day or two and, although reasonably good analytical figures are obtained on a freshly prepared sample, after six months' storage the carbon content increases and the nickel content falls considerably; the catalytic activity also falls off markedly on storage.

Of a range of compounds investigated, only three acetylenic compounds were successfully trimerised; propargyl alcohol (see Reppe and Schweckendiek, *loc. cit.*), phenylethynylcarbinol (1-phenylpropargyl alcohol), and phenylacetylene. Phenylethynylcarbinol in boiling methyl alcohol was slowly trimerised to 1 : 3 : 5-*tri*-(α-*hydroxybenzyl*)*benzene*, the structure of which was demonstrated by its oxidation to the known *s*-tribenzoylbenzene. The polymerisation of phenylacetylene by the catalyst was violent and, unless the compound was diluted with a large volume of alcohol, was almost explosive. In 10% alcoholic solution, polymerisation is vigorous and exothermic, but can be controlled. The crude product, an orange-brown gum, was purified by distillation and repeated crystallisation, giving a white crystalline solid, m. p. 109°, with the molecular weight and the composition of a triphenylbenzene. Of the three theoretically possible triphenylbenzenes, only the 1 : 2 : 3-, m. p. 157° (Smith, *Ber.*, 1893, **26**, 65), and the 1 : 3 : 5-isomer, m. p. 170° (Vorländer, Fischer, and Wille, *Ber.*, 1929, **62**, 2836), are known. The hydrocarbon, m. p. 109°, was clearly different from either of these; the m. p. of *s*-triphenylbenzene was depressed to 80°—90° on admixture, and the formation of 1 : 2 : 3-triphenylbenzene would be very improbable, involving as it would the migration of a phenyl radical under relatively mild conditions. By elimination, therefore, it appeared probable that the substance in hand was the hitherto unknown 1 : 2 : 4-*triphenylbenzene*. This was established by synthesis, as follows



(I.) (II.) (III.) (IV.)

4-Hydroxy-3 : 4-diphenyl*cyclo*pent-2-en-1-one (I) (Japp and Miller, *J.*, 1885, 27) ("anhydromonoacetone benzil"), when heated with styrene in the presence of potassium hydrogen sulphate as dehydrant, affords the adduct 3 : 6-endo*keto*-1 : 2 : 4-*triphenyl*cyclo*hex*-1-*ene* (II), which on being heated above its melting point loses carbon monoxide and gives (presumably) a triphenyldihydrobenzene (*e.g.*, III), which could not be obtained crystalline but which, when dehydrogenated with sulphur, gave 1 : 2 : 4-triphenylbenzene (IV) identical with that obtained by polymerisation of phenylacetylene. Attempts to simplify the synthesis by interaction of (I) and phenylacetylene, which should have given (IV) more directly, *via* the (unstable) doubly unsaturated analogue of (II), were unsuccessful.

The formation of 1 : 2 : 4-triphenylbenzene unaccompanied by the 1 : 3 : 5-isomer is peculiar; Krasouskii and Kipryanov (*J. Phys. Chem. Russia*, 1925, **56**, 1; from *Chem. Abs.* 1925, **19**, 2817) showed that phenylacetylene, when heated with methylamine or ethylamine at 250—260° for 5—6 hours (sealed tube), affords *s*-triphenylbenzene. It is virtually certain that the *s*-isomer is

not formed in the polymerisation described here; its solubility is much lower than that of the 1 : 2 : 4-isomeride, and it is clear that if both were formed together, the *s*-isomeride would be the more easily isolated. Attempted trimerisation of a variety of other ethynyl compounds, including 3-methylbut-1-yn-3-ol, 3-diethylaminobut-1-yne, benzoylacetylene, and phenylpropiolic acid, all failed or gave non-crystalline products which could not be identified.

Experimental.

Dicarbonyldi(triphenylphosphino)nickel, $[(CO)_2Ni(Ph_3P)_2]$.—Triphenylphosphine (13·1 g.) in ether (30 c.c.) was refluxed gently on the steam-bath, and nickel carbonyl (4·2 g.; 3·2 c.c.) was gradually added. Carbon monoxide was evolved briskly and, after addition of half of the nickel carbonyl, crystals were deposited from the solution. When addition of the nickel carbonyl was complete, the mixture was refluxed for a further 30 minutes, cooled, and filtered. Dicarbonyldi(triphenylphosphino)nickel (13·9 g.) was obtained as a pale cream-coloured crystalline solid, m. p. 210—215° (decomp.) when plunged into a bath preheated to 210° (Reppe and Schweckendiek, *loc. cit.*, gave m. p. 206—209°) (Found: C, 70·7; H, 5·0; Ni, 8·5. Calc. for $C_{38}H_{30}O_2P_2Ni$: C, 71·3; H, 4·7; Ni, 9·2%).

s-Tri-(o-hydroxybenzyl)benzene.—Phenylethynylcarbinol (1-phenylpropargyl alcohol) (10 g.) and the catalyst (0·5 g.) were refluxed in methyl alcohol (10 c.c.) overnight; there was no exothermic reaction. Evaporation of the solution, finally at 100°/16 mm., gave a brown gum which slowly crystallised; trituration with ether gave a cream-coloured solid (1·6 g.), m. p. 160—173°, which after repeated crystallisation from benzene afforded 1 : 3 : 5-*tri-(o-hydroxybenzyl)benzene*, m. p. 181° (Found: C, 81·3; H, 6·2. $C_{27}H_{24}O_3$ requires C, 81·8; H, 6·1%).

s-Tribenzoylbenzene.—The above trimer (0·35 g.) in acetone (5 c.c.) was oxidised by dropwise addition of chromium trioxide (0·2 g.) in water (0·6 c.c.) containing sulphuric acid (0·2 g.). The temperature rose spontaneously to 40°, and after 30 minutes' stirring water was added and the precipitated solid was collected (0·32 g.; m. p. 113—115°). One recrystallisation from alcohol afforded *s*-tribenzoylbenzene, m. p. 117°, undepressed by admixture with an authentic specimen, m. p. 116—118° (Found: C, 83·1; H, 4·2. Calc. for $C_{27}H_{18}O_3$: C, 83·1; H, 4·6%).

1 : 2 : 4-*Triphenylbenzene*. *Polymerisation of Phenylacetylene*.—Phenylacetylene (10 g.) in alcohol (100 c.c.) was heated under reflux on the steam-bath with the catalyst (0·5 g.). At 70° (internal temperature) a violent reaction occurred which was checked by cooling; when this had subsided the mixture was boiled under reflux for 1 hour, a dark oil separating. The mixture was poured into water and the oil extracted with ether, dried, and distilled. Fractions (*a*), b. p. about 160°/0·15 mm., and (*b*), b. p. about 190°/0·15 mm., were collected. Fraction (*a*) solidified and after 3 recrystallisations from alcohol afforded 1 : 2 : 4-*triphenylbenzene* as colourless prisms, m. p. 109° (Found: C, 94·25; H, 5·85; *M*, cryoscopic in benzene, 303. $C_{24}H_{18}$ requires C, 94·1; H, 5·9%; *M*, 306). Fraction (*b*), an orange viscous oil, deposited some crystalline material on cooling. It was dissolved in alcohol and cooled, and the mother-liquor decanted. Spontaneous evaporation of the liquor gave a yellow amorphous solid which on repeated recrystallisation from alcohol, and finally from light petroleum, gave white crystals, m. p. 109°, identical with those from fraction (*a*).

3 : 6-*endo*-*Keto*-1 : 2 : 4-*triphenylcyclohex*-1-*ene*.—4-Hydroxy-3 : 4-diphenyl*cyclo*pent-2-en-1-one ("anhydromonoacetone benzil") (10 g.; Japp and Miller, *loc. cit.*), potassium hydrogen sulphate (10 g.), and styrene (20 g.) were refluxed for 2·5 hours. The hot supernatant styrene solution was decanted from the cake of potassium hydrogen sulphate, cooled, and diluted with ether. A pale yellow solid (5·25 g.), m. p. 183—184°, separated. Recrystallisation from alcohol–acetone gave white needles of 3 : 6-*endo*-*keto*-1 : 2 : 4-*triphenyl*cyclo*hex*-1-*ene*, m. p. 188° with effervescence (Found: C, 89·2; H, 5·95. $C_{32}H_{26}O$ requires C, 89·3; H, 5·95%).

When heated at 220—230°, 3 : 6-*endo*keto-1 : 2 : 4-triphenyl*cyclo*hex-1-ene (5 g.) evolved carbon monoxide briskly. The resulting yellow gum could not be induced to crystallise, and was mixed with powdered sulphur (1 g.) and heated at 250° for 4 hours. The product was distilled (b. p. about 170°/0·1 mm.) giving an orange viscous oil, which was dissolved in light petroleum (b. p. 60—80°) and set aside. After 3 days clusters of crystals separated; these were recrystallised twice from light petroleum, sublimed at 100°/0·1 mm., and finally recrystallised, giving white crystals of 1 : 2 : 4-triphenylbenzene, m. p. 109°, undepressed by admixture with material obtained from the polymerisation of penylacetylene.

The authors are indebted to their colleague, Mr. H. P. W. Huggill, for the suggestion for the synthesis of the triphenylbenzene.

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Hexagon House, Manchester, 9. [*Received, September 28th*, 1949.]

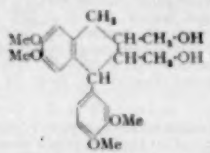
17. *The Constituents of Natural Phenolic Resins. Part XXII. Reduction of Some Lactonic Lignans with Lithium Aluminium Hydride.*

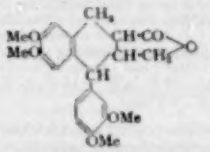
By Robert D. Haworth and Leslie Wilson.

The "trans-"configuration previously assigned to (−)-matairesinol and (−)-hinokinin has been confirmed by reduction with lithium aluminium hydride to optically active diols; (+)-*iso*matairesinol has a "cis-"configuration and gives a *meso*diol on reduction. (−)-Conidendrin dimethyl ether has been reduced to (+)-*iso*lariciresinol dimethyl ether.

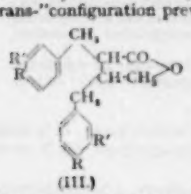
The introduction of lithium aluminium hydride as a reagent for the conversion of lactones into diols (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738) suggested several applications in the lignan field, and the present communication describes a number of stereochemical relations which have been established or confirmed by the use of this reagent.

The conversion of (+)-*iso*lariciresinol dimethyl ether (I) into (−)-conidendrin dimethyl ether (II) was reported in an earlier paper (*J.*, 1937, 384), and the reverse change has now been realised by the use of lithium aluminium hydride in ether–benzene, thereby confirming the close stereochemical relation of the two lignans.


(I.)


(II.)

In earlier communications (*J.*, 1938, 797, 1985; 1939, 154, 1054; 1940, 1098), evidence was brought forward suggesting that (−)-matairesinol (III; R = OH, R′ = OMe) has a "trans-" configuration, and the corresponding "cis-"arrangement was assigned to (+)-*iso*matairesinol. These conclusions have now been confirmed by the reduction of (−)-matairesinol dimethyl ether (III; R = R′ = OMe) and (+)-*iso*matairesinol dimethyl ether into the (−) and *meso*-forms of **1 : 4-*di*-(3 : 4-*dimethoxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane*** (IV; R = R′ = OMe), respectively. In the same way (−)-hinokinin (III; RR′ = CH_2O_2) has been reduced to (−)-**1 : 4-*di*-(3 : 4-*methylenedioxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane*** (IV; RR′ = CH_2O_2), identical with "dihydrocubebin" (Bruchhausen and Gerhard, *Ber.*, 1939, **72**, 830), thus confirming the "trans-"configuration previously advanced for (−)-hinokinin.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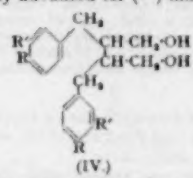
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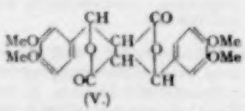
(V.)

Several attempts to reduce the synthetic dilactone (V) (*J.*, 1944, 535) have been made; so far we have failed to isolate crystalline material, but this synthetical route to pinoresinol dimethyl ether is still under investigation.

Experimental.

(+)-*iso*Lariciresinol *Dimethyl Ether* (I).—Cold solutions of (−)-conidendrin dimethyl ether (1 g.) in benzene (40 c.c.) and of lithium aluminium hydride (0·5 g.) in ether (40 c.c.) were mixed and allowed to react for 2 hours, during which a white gelatinous precipitate separated. The bulk of the solvent was reduced to about 40 c.c. by distillation under reduced pressure, and the precipitated metal alkoxide decomposed by careful addition of dilute hydrochloric acid. The benzene layer was washed twice with water, dried ($CaCl_2$), and evaporated to dryness. The product (0·85 g.) separated from aqueous methyl alcohol in colourless needles, m. p. 167—168°, $[\alpha]_D^{20}$ + 18° (*c*, 1·8272 in chloroform) (cf. *J.*, 1937, 384; m. p. 166—167°, $[\alpha]_D^{20}$ + 20° in chloroform). Anhydro*iso*lariciresinol dimethyl ether, obtained by heating the above diol (I) (0·2 g.) with potassium hydrogen sulphate (0·4 g.) at 180° for ½ hour, crystallised from methyl alcohol in colourless prisms (0·13 g.), m. p. 147—148°, $[\alpha]_D^{20}$ − 33·9° (*c*, 0·3840 in acetone) (cf. *J.*, 1937, 384; m. p. 146—147°, $[\alpha]_D^{20}$ − 33·4° in acetone).

(−)-**1 : 4-*Di*-(3 : 4-*dimethoxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane*** (IV; R = R′ = OMe).—(−)-Matairesinol dimethyl ether (1 g.) in benzene (30 c.c.) and lithium aluminium hydride (0·5 g.) in ether (30 c.c.) were allowed to react for 2 hours. The volume of the solvent was reduced by distillation, dilute hydrochloric acid was added, and the product from the washed and dried benzene layer was crystallised from methyl alcohol containing a little ether in colourless prisms (0·88 g.), m. p. 119—120°, $[\alpha]_D^{20}$ − 29·6° (*c*, 0·4380 in chloroform) (cf. *J.*, 1939, 1054; m. p. 121—122°, $[\alpha]_D^{20}$ − 26·2° in chloroform). (−)-**3 : 4-Di-(3 : 4-dimethoxybenzyl)tetrahydrofuran**, obtained by heating the above diol (0·15 g.) with potassium hydrogen sulphate (0·3 g.) at 180° for ½ hour, separated from methyl alcohol in colourless prisms (0·11 g.), m. p. 117—118°, $[\alpha]_D^{20}$ − 54·5° (*c*, 0·0928 in chloroform) (cf. *J.*, 1939, 1054; m. p. 118—119°, $[\alpha]_D^{20}$ − 58·9° in chloroform).

meso-**1 : 4-*Di*-(3 : 4-*dimethoxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane*.**—(+)-iso*Matairesinol* dimethyl ether (0·1 g.) in benzene (5 c.c.) was treated with cold lithium aluminium hydride (0·05 g.) in ether (5 c.c.). After 2 hours the volume was reduced by distillation under reduced pressure, and dilute hydrochloric acid was added. The product, isolated from the benzene layer, crystallised from methyl alcohol in colourless prisms (0·079 g.), m. p. 94—95°, [α] 0° (*c*, 0·1881 in chloroform) (Found: C, 67·5; H, 7·5. $C_{20}H_{26}O_6$ requires C, 67·7; H, 7·7%).

meso-**3 : 4-*Di*-(3 : 4-*dimethoxybenzyl*)*tetrahydrofuran***, obtained by heating the *meso*-diol (0·06 g.) with potassium hydrogen sulphate (0·12 g.) at 180° for 0·5 hours, separated from methyl alcohol in colourless prisms (0·05 g.), m. p. 114—115°, [α] 0° (*c*, 0·0884 in chloroform) (Found: C, 70·8; H, 7·7. $C_{20}H_{24}O_5$ requires C, 70·6; H, 7·6%).

(−)-**1 : 4-*Di*-(3 : 4-*methylenedioxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane*** (IV; RR′ = CH_2O_2).—(−)-Hinokinin (1 g.) in benzene (50 c.c.) was mixed with a solution of lithium aluminium hydride (0·5 g.) in ether (50 c.c.). After 2 hours, dilute hydrochloric acid was added, and the diol, isolated from the benzene layer, separated from ether–light petroleum (b. p. 60—90°) in colourless needles (0·93 g.), m. p. 102—103°, $[\alpha]_D^{20}$ − 34° (*c*, 0·8476 in chloroform) (Bruchhausen and Gerhard, *loc. cit.*, give m. p. 104°, $[\alpha]_D^{20}$ − 30·6° in chloroform). (−)-**3 : 4-*Di*-(3 : 4-*methylenedioxybenzyl*)*tetrahydrofuran***, formed by heating the above diol (0·2 g.) with potassium hydrogen sulphate (0·4 g.) at 180° for ½ hour, was distilled at 0·5 mm. (bath temperature, 280—300°) and crystallised from ether–light petroleum (b. p. 60—90°) in colourless prisms (0·14 g.), m. p. 52—52·5° $[\alpha]_D^{20}$ − 58·3° (*c*, 0·1716 in chloroform) (Found: C, 70·6; H, 6·2. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

Our thanks are due to the Department of Scientific and Industrial Research for a maintenance grant, and to Messrs. Imperial Chemical Industries, Limited, for a grant for the purchase of materials.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, September 28th* 1949.]

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18. *Experiments with Diazomethane and its Derivatives. Part XV. Action of Diazomethane on o-Quinone Monoximes.*

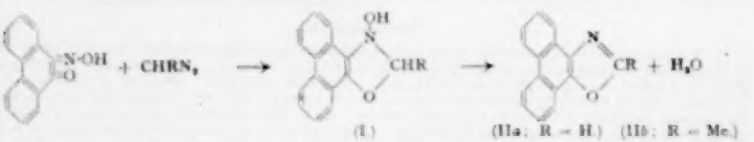
By ALEXANDER SCHÖNBERG and WILLIAM IBRAHIM AWAD.

Reaction of the monoximes of phenanthraquinone, retenequinone, and chrysenequinone with diazomethane or diazoethane leads to oxazole derivatives. Oxazoline derivatives corresponding to the intermediate (I) were found in the case of acenaphthenequinone monoxime, triketoindane-2 oxime, and 2-oximino-3 : 3-diphenylindan-1-one.

A scheme is advanced showing the similarity of the action of diazomethane on diketones, *o*-quinones, α-keto-lactones, *o*-quinone imines and monoximes, ketomethylene derivatives, and thioures.

VERY little is known about the action of diazomethane on *o*-quinone monoximes. It is stated, however, that oximinocamphor (stable or unstable form) gives, with diazomethane, the *N*-methyl ether (Forster and Holmes, *J.*, 1908, **93**, 247).

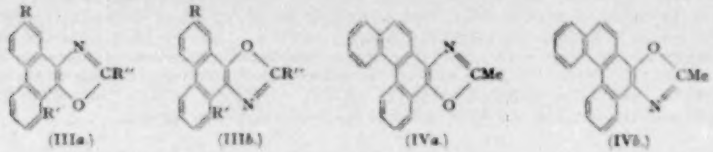
When phenanthraquinone monoxime was treated with diazomethane, phenanthroxazole (IIa) was obtained by loss of water from an intermediate product (I), which was not isolated. The action of diazoethane led to 2-methylphenanthroxazole (IIb).



(I) (IIa; R = H.) (IIb; R = Me.)

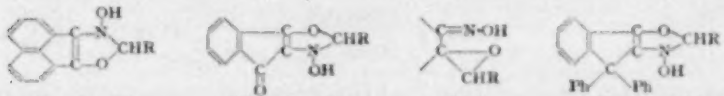
Diazomethane with retenequinone monoxime yielded reteno-oxazole (IIIa or *b*; R = Me, R′ = Pr^i, R″ = H), the uncertainty being caused by lack of knowledge of the position of the oximino-group present in retenequinone monoxime. Diazoethane similarly yields 2-methyl-

reteno-oxazole (IIIa or *b*; R = Me, R′ = Pr^{i}, R″ = Me). The products (III) are identical with those previously obtained from retenequinone imine. Schönberg and Awad (*J.*, 1947, 651)



(IIIa.) (IIIb.) (IVa.) (IVb.)

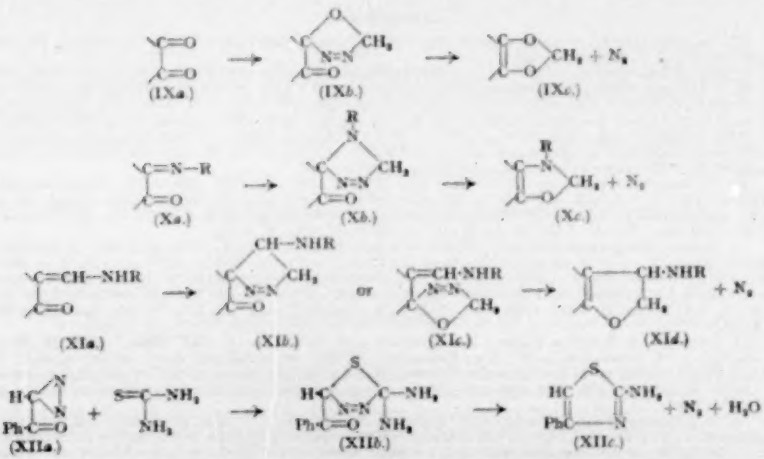
pointed out the uncertainty concerning the structure of reteno-oxazoles, but defined it incorrectly in formulæ (II)—(IV) of that paper.



(Va; R = H.) (Vb; R = Me.) (VIa; R = H.) (VIb; R = Me.) (VII.) (VIIIa; R = H.) (VIIIb; R = Me.)

Diazoethane and chrysenequinone monoxime similarly give the 2-methylchryseno-oxazole (IVa or *b*).

Diazomethane and acenaphthenequinone monoxime or triketoindane-2 oxime give **3-*hydroxy-acenaphthyleno*(7′ : 8′-4 : 5)*oxazoline*** (**Va**) or **3-*hydroxy*-1′-*ketoindeno*(2′ : 3′-4 : 5)*oxazoline*** (**VIa**). (**Va**) and (**VIa**) are pale yellow substances. They contain no methoxy-group and only one active hydrogen atom (Zeisel's method). Acid hydrolysis of (**Va**) gives acenaphthenequinone, probably owing to the oxidation of the intermediate **1 : 2**-dihydroxyacenaphthylene. (**VIa**) similarly yields triketoindane hydrate (ninhydrin). The results of hydrolysis make it improbable that the heterocyclic rings in (**Va**) and (**VIa**) can be replaced by (VII), since such substances are not expected to be hydrolysed in acid to acenaphthenequinone and triketoindane which would necessitate the rupture of a C–C linkage. According to Wanag and Lode (*Ber.*, 1939, **72**, 49) triketoindane 2-oxime is to be formulated as 2-nitrosoindane-1 : 3-dione but in our opinion its pale yellow colour is not in agreement with this hypothesis. (**Vb**) and (**VIb**) were obtained by use of diazoethane.



(IXa.) (IXb.) (IXc.)

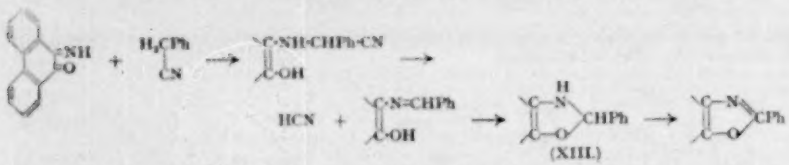
(Xa.) (Xb.) (Xc.)

(XIa.) (XIb.) (XIc.) (XId.)

(XIIa.) (XIIb.) (XIIc.)

The action of diazomethane on 2-oximino-3 : 3-diphenylindan-1-one yielded 3-*hydroxy*-1′ : 1′-*diphenylindeno*(2′ : 3′-4 : 5)*oxazoline* (VIIIa), a pale yellow substance containing one active hydrogen atom; with diazoethane the 2-*methyl* derivative (VIII*b*) was obtained.

The formation of five-membered ring compounds by the action of diazomethane and its derivatives on 1 : 2-diketones, *o*-quinones, α-keto-lactones (cf. IX*a* ⟶ IX*c*), *o*-quinone imines and monoximes (cf. X*a* ⟶ X*c*; R = H or OH), ketomethylene derivatives (cf. XI*a* ⟶ XI*d*), and thiourea (cf. XII*a* ⟶ XII*c*) may all be regarded as proceeding according to the same scheme, *i.e.*, addition of diazomethane to the >C⟹O, >C⟹N⟝, >C⟹C<, or >C⟹S group (cf. IX*b* and XI*c*, X*b*, XI*b*, and XII*b*), followed by the elimination of nitrogen.



For the action of diazomethane on 1 : 2-diketones, *o*-quinones, coumarandiones, and thiocoumarandiones see Biltz and Paetzold (*Annalen*, 1923, **433**, 71), Arndt, Amende, and Ender (*Monatsh.*, 1932, **59**, 202), Fieser and Hartwell (*J. Amer. Chem. Soc.*, 1935, **57**, 1479), and Schönberg, Moubasher, and Mostafa (*J.*, 1941, 348). For the action on quinone imines (X*a*; R = H) see Schönberg and Awad (*loc. cit.*); the products actually obtained (*e.g.*, IIa in the case of phenanthraquinone-imine and diazomethane) are oxazole derivatives formed by dehydrogenation of the intermediate products (*e.g.*, XIII, but with H replacing Ph). Reaction (X*a* ⟶ X*c*; R = OH) is described in this paper. For (XI*a* ⟶ XI*d*) see Schönberg, Mustafa, and Hilmy (*J.*, 1947, 1946). For the formation of (XII*c*) see King and Miller (*J. Amer. Chem. Soc.*, 1949, 367), who however do not discuss the formation of (XII*b*).

In connection with the synthesis of the phenanthroxazole derivatives, we have obtained 2-phenylphenanthroxazole (II, R = Ph) by the action of benzyl cyanide or deoxybenzoin on phenanthraquinone imine. In the case of benzyl cyanide the reaction is believed to proceed according to to the scheme above, and a similar one is proposed for the action of deoxybenzoin. The dehydrogenation required in the last step may be due to the oxidation by atmospheric oxygen or a second molecule of phenanthraquinone imine (Schönberg and Awad, *loc. cit.*). The action of *p*-nitrobenzyl cyanide leads to the formation of 2-*p*-nitrophenylphenanthroxazole.

Experimental.

The ethereal solution of diazomethane (diazoethane) was prepared according to *Org. Synth.*, Vol. 15, p. 3 (Werner, *J.*, 1919, **115**, 1093).

Action of Diazomethane on Oximes.—(a) *Phenanthraquinone monoxime* (Goldschmidt, *Ber.*, 1883, **16**, 2178). The oxime (0·5 g.) was suspended in ether and treated with an excess of ethereal diazomethane as usual for 6 hours. The solution was evaporated to dryness *in vacuo*, and the residue recrystallised from methyl alcohol; phenanthroxazole (IIa) was obtained in light-yellow crystals, m. p. 152° (Found: C, 81·8; H, 4·0; N, 6·4. Calc. for $C_{15}H_9ON$: C, 82·2; H, 4·1; N, 6·4%). A mixed-m. p. determination with phenanthroxazole prepared according to Schönberg and Awad (*loc. cit.*) gave no depression; both samples gave the same colour with concentrated sulphuric acid.

(b) *Retenequinone monoxime* (Bamberger and Hooker, *Annalen*, 1885, **200**, 102). Reteno-oxazole (IIIa or IIIb; R = Me, R′ = Pr^i, R″ = H) recrystallised from methyl alcohol in yellow crystals, m. p. 108°, undepressed on admixture with an authentic specimen (Schönberg and Awad, *loc. cit.*) (Found: C, 82·7; H, 6·1; N, 5·2. Calc. for $C_{18}H_{17}ON$: C, 82·9; H, 6·2; N, 5·1%).

(c) *Acenaphthenequinone monoxime* (Francesconi and Pirazzoli, *Gazzetta*, 1903, **33**, I, 36). 3-*Hydroxyacenaphthyleno*(7′ : 8′-4 : 5)*oxazoline* (Va) recrystallised from methyl alcohol in yellow crystals, m. p. 163°. It gives a yellowish-orange colour in concentrated sulphuric acid, is insoluble in concentrated aqueous sodium hydroxide solution, and sublimes *in vacuo* (boiling ethyl cinnamate bath) (Found: C, 73·4; H, 4·3; N, 6·8; active H, 0·58; OMe, nil. $C_{13}H_9O_2N$ requires C, 73·9; H, 4·3; N, 6·6; one active H, 0·47%).

(d) 2-*Oximino*-3 : 3-*diphenylindan*-1-*one* (Koelsch and Le Claire, *J. Org. Chem.*, 1941, **6**, 531). 3-*Hydroxy*-1′ : 1′-*diphenylindeno*(2′ : 3′-4 : 5)*oxazoline* (VIIIa) recrystallised from methyl alcohol in light-yellow crystals, m. p. 178° (Found: C, 80·0; H, 5·1; N, 4·5; active H, 0·3. $C_{28}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3; one active H, 0·3%). It gave a yellowish-orange colour in concentrated sulphuric acid.

(e) *Triketoindane* 2-*oxime* (Teeters and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 3026). 3-*Hydroxy*-1′-*ketoindeno*(2′ : 3′-4 : 5)*oxazoline* (VIa) was obtained in a way similar to that described previously, but ½ hour after the addition of the diazomethane solution a green deposit was formed which was filtered off. After recrystallisation twice from ethyl alcohol (96%) and then from methyl alcohol, yellow crystals of (VIa)

were obtained, having m. p. 247° (to a reddish-brown melt; shrinking before melting) (Found: C, 63·4; H, 4·0; N, 7·87; OMe, nil. $C_{16}H_7O_3N$ requires C, 63·5; H, 3·7; N, 7·4%). It gave a yellowish-orange colour with concentrated sulphuric acid.

Hydrolysis of 3-*Hydroxyacenaphthyleno-oxazoline*.—The substance (0·2 g.) was dissolved in hot methyl alcohol (10 c.c.), and then concentrated hydrochloric acid (10 c.c.) was added. The mixture was refluxed for 2 hours and left to cool; the brown precipitate recrystallised from glacial acetic acid in yellow crystals which proved to be acenaphthenequinone, the m. p. being undepressed on admixture with an authentic specimen; both samples gave the same colour with concentrated sulphuric acid.

Hydrolysis of (VIa).—The substance (VIa) (0·1 g.) was dissolved in glacial acetic acid (15 c.c.), and an equal volume of concentrated hydrochloric acid was added. The mixture was refluxed for 4 hours. The solution was evaporated under normal pressure till a solid began to appear, and then cooled and filtered. The product was impure ninhydrin, as it gave a violet colour on the skin in the presence of water. The substance when treated with concentrated sodium hydroxide solution gave the blue colour reaction of ninhydrin.

Action of Diazoethane on Oximes.—(a) *Phenanthraquinone monoxime*. The oily residue obtained after the ether had been distilled off was cooled and scratched, with a little dilute methyl alcohol; it solidified to a brownish amorphous mass, which crystallised from methyl alcohol in light-yellow crystals, m. p. 145°, undepressed on admixture with an authentic specimen of 2-methylphenanthroxazole (IIb), prepared according to Schönberg and Awad (*loc. cit.*) (Found: C, 82·6; H, 4·8; N, 5·7. Calc. for $C_{14}H_{11}ON$: C, 82·4; H, 4·7; N, 6·0%).

(b) *Retenequinone monoxime*. 2-Methylreteno-oxazole (III; R = Me, R′ = Pr^i, R″ = Me) recrystallised from dilute methyl alcohol (80%) in light-yellow crystals, m. p. 135°, undepressed on admixture with an authentic specimen prepared according to Schönberg and Awad (*loc. cit.*) (Found: C, 83·4; H, 6·7; N, 4·7. Calc. for $C_{20}H_{19}ON$: C, 83·0; H, 6·6; N, 4·8%).

(c) *Chrysenequinone monoxime* (Graebe and Hönigsberger, *Annalen*, 1900, **311**, 272). 2-*Methylchrysenenaphthoxazole* (IVa or *b*) recrystallised from methyl alcohol in yellow crystals, m. p. *ca.* 223° (Found: C, 84·9; H, 4·9; N, 4·5. $C_{20}H_{13}ON$ requires C, 84·8; H, 4·6; N, 4·9%).

(d) *Acenaphthenequinone monoxime*. 3-*Hydroxy*-2-*methylacenaphthylene*(7′ : 8′-4 : 5)*oxazoline* (Vb) recrystallised from methyl alcohol in yellow crystals, m. p. 93°, and gave an orange colour in concentrated sulphuric acid (Found: N, 6·4; active H, 0·48. $C_{14}H_{11}O_2N$ requires N, 6·2; one active H, 0·44%).

(e) 2-*Oximino*-3 : 3-*diphenylindan*-1-*one*. 3-*Hydroxy*-1′ : 1′-*diphenyl*-2-*methylindeno*(2′ : 3′-4 : 5)-*oxazoline* (VIIIb) crystallised from methyl alcohol in yellow crystals, m. p. 152° (Found: C, 80·7; H, 5·6; N, 3·9. $C_{29}H_{19}O_2N$ requires C, 80·9; H, 5·6; N, 4·1%). It gave an orange colour with concentrated sulphuric acid.

(f) *Triketoindane* 2-*oxime*. 3-*Hydroxy*-1′-*keto*-2-*methylindeno*(2′ : 3′-4 : 5)*oxazoline* (VIb) crystallised from methyl alcohol in yellow crystals, m. p. 160°, insoluble in cold sodium hydroxide solution (Found: C, 64·9; H, 4·5. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·4%).

Action of (a) *Benzyl Cyanide*, (b) *Deoxybenzoin, and* (c) p-*Nitrobenzyl Cyanide on Phenanthraquinone Imine*.—(a) The imine (0·5 g.) and benzyl cyanide (0·3 g.) in anisole (5 c.c.) were refluxed for 1 hour, after which the anisole was evaporated off. The residual brown oil was cooled in an ice–salt mixture and triturated with alcohol (98%) at that temperature, whereby a yellow solid was formed. The product (II; R = Ph), crystallised from ethyl alcohol, had m. p. 202°, undepressed on admixture with an authentic specimen of 2-phenylphenanthroxazole prepared according to Stein and Day (*J. Amer. Chem. Soc.*, 1942, **64**, 2567) (Found: C, 85·1; H, 4·5; N, 4·6. Calc. for $C_{21}H_{13}ON$: C, 85·4; H, 4·4; N, 4·8%).

(b) The reaction was carried out as above, and the 2-phenylphenanthroxazole produced, after crystallisation from ethyl alcohol, had m. p. 202°, undepressed on admixture with the product obtained in (a) (Found: C, 85·4; H, 4·8; N, 4·8%).

(c) p-*Nitrobenzyl cyanide*. The reaction was carried out as in (a) with the imine (0·5 g.) and *p*-nitrobenzyl cyanide (0·5 g.). 2-*p*-Nitrophenylphenanthroxazole (II; R = *p*-$NO_2{\cdot}C_6H_4$) obtained on cooling the mixture was crystallised from chloroform as yellow crystals, m. p. 268° (Found: C, 74·1; H, 3·6; N, 7·8. Calc. for $C_{21}H_{12}O_3N_2$: C, 74·3; H, 3·5; N, 8·2%). Schiedt (*J. pr. Chem.*, 1941, **157**, 203) gives m. p. 272°.

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19. *The Physical Properties of Some Aliphatic Compounds.*

By S. A. MUMFORD and J. W. C. PHILLIPS.

Measurements are reported of the densities, refractive indices, surface tensions, and viscosities, at 20° and 25° whenever practicable, of a number of aliphatic compounds of different types.

The results are briefly discussed from the standpoint of the parachor thesis previously advanced (*J.*, 1929, 2112).

IN the decade following publication of a paper on the evaluation and interpretation of parachors (*J.*, 1929, 2112) the authors undertook, as opportunity arose, the determination of the surface tension and other physical properties of a number of aliphatic compounds, with the object of obtaining further evidence in support of the thesis then advanced, namely that the CH_2 parachor increment of 39 units originally adopted by Sugden (*J.*, 1924, **125**, 1177) was too small and should be replaced by one of 40 units, and that constitutive deviations from parachor additivity

could be accounted for by the systematic introduction of "strain constants." The investigation was interrupted by the war, and as circumstances have since arisen which make it impossible to resume the collaboration, it has been thought desirable to place on record the results obtained up to 1939.

The original aim of the investigation was twofold: (i) to obtain a representative value for the CH_2 increment by examining the average parachor increase over a considerable CH_2 interval in a number of different aliphatic series; and (ii) to obtain more detailed information on the magnitude of the parachor defect associated with accumulation of negative groups in a molecule, particularly on one carbon atom. With the first object in view, a series of *n*-hexadecyl compounds was prepared, and their parachors, determined at uniform temperature as far as practicable, were compared with those of the corresponding *n*-butyl derivatives. Later, examination was made of a number of intermediate members in some of the series, to check the atomic or group constants concerned. The second aim of the investigation involved measurement of the parachors of a number of polyhalogenated hydrocarbons, ethers, and sulphides, and of a series of alkyl mono-, di-, and tri-chloroacetates, and αω-dihalogeno- and -dicarbethoxy-alkanes.

Experimental.

Many of the compounds were purified from commercially available materials (generally from Messrs. British Drug Houses or Schering-Kahlbaum). As regards the others, the methods of preparation employed were those in general use. Thus, the *n*-alkyl halides were prepared from the corresponding purified alcohols by treatment with the requisite phosphorus halide. (In the case of the *n*-amyl compounds, the alcohol was synthesised from purified *n*-butyl bromide, which was also the starting point for the preparation of synthetic *n*-valeric acid.) The chlorinated esters were obtained by esterification of the appropriate acid with the requisite purified alcohol, and the alkyl 2-chloroethyl ethers by the action of methyl or ethyl sulphate on ethylene chlorohydrin. 2 : 2′-Dichlorodiethyl ether was prepared in a manner analogous to that used by Kamm and Waldo (*J. Amer. Chem. Soc.*, 1921, **43**, 2223), and pentachlorodiethyl ether by treating the condensation product of chloral and ethylene chlorohydrin with phosphorus pentachloride (Henry, *Ber.*, 1874, **7**, 763). Tetra- and penta-methylene dichloride were prepared from adipamide and piperidine, respectively, by the method of von Braun (*Ber.*, 1905, **38**, 2340; 1906, **39**, 4119). The *n*-alkyl sulphides were obtained by the action of sodium sulphide on the appropriate alkyl bromide, and 2-chlorodiethyl sulphide by the action of thionyl chloride on the condensation product of sodium thioethoxide and ethylene chlorohydrin (Mayer, *Annalen*, 1877, **240**, 310). All the products were purified to constant properties by repeated fractionation through a Young column. The preparation of the *n*-hexadecyl compounds and of the polychlorinated sulphides has already been reported (*J.*, 1931, 1732; 1929, 535). See also *Rec. Trav. chim.*, 1933, **52**, 175, 181, and *J.*, 1934, 1657 for the preparation of the higher ethyl esters, alcohols, and acetates.

Refractive indices were measured, at 20° whenever possible, with a calibrated Abbé refractometer. The other physical properties were determined at two temperatures (20° and 25° where practicable), the values quoted being the means of at least two determinations, made with different apparatus, at each temperature. The densities were determined with water-calibrated specific-gravity bottles, all weighings being reduced to a vacuum; the surface tensions were measured by Sugden's modification of the maximum bubble-pressure method (*J.*, 1922, **121**, 860), using bubblers calibrated with pure benzene (f. p. 5·5°, b. p. 80·2°, d_4^{20} 0·8790, n_D^{20} 1·5012), taking γ_{20} = 28·88 dynes/cm.; the viscosities were determined in small Ostwald-type viscometers conforming in general characteristics to the standards laid down in British Standard Specification No. 188—1929, and calibrated with water and/or standard sugar solutions.

Results.

Compound.	F. p.	B. p. (760 mm. except where stated).	*t.*	d_4^t.	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
2 : 5-Dimethylhexane	—	109·2°	20°	0·6994	1·3933	38·98	19·9	344·7	0·485
			25	0·6959	—	—	19·4	344·2	0·456
n-Decane	—	173·3	20	0·7307	1·4116	48·37	24·0	430·8	0·920
			25	0·7270	—	—	23·5	430·6	0·855
n-Hexadecane	17·6°	285·8	20	0·7746	1·4350	76·22	27·8	670·7	3·53
			25	0·7712	—	—	27·35	670·9	3·10
n-Hexadec-1-ene	—	159·5 (21 mm.)	20	0·7825	1·4428	75·95	27·9	658·7	3·09
			25	0·7792	—	—	27·45	658·8	2·76
n-Propyl chloride	—	46·5	20	0·8890	1·3900	20·94	22·15	191·6	0·355
			25	0·8830	—	—	21·5	191·5	0·337
n-Butyl chloride	—	78·4	20	0·8866	1·4021	25·42	23·75	230·4	0·450
			25	0·8811	—	—	23·1	230·2	0·427
*iso*Butyl chloride	—	68·4	20	0·8780	1·3978	25·42	21·95	228·1	0·457
			25	0·8725	—	—	21·4	228·1	0·431

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	*t*.	d_4^t	n_D^t	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
n-Amyl chloride	—	107·9°	20°	0·8840	1·4125	30·02	25·15	269·9	0·580
			25	0·8795	—	—	24·55	269·7	0·547
tert.-Amyl chloride	—	85·6	20	0·8659	1·4050	30·16	22·3	267·4	0·599
			25	0·8612	—	—	21·8	267·3	0·560
n-Hexyl chloride	—	134·3	20	0·8790	1·4195	34·67	26·15	310·2	0·743
			25	0·8745	—	—	25·55	310·0	0·696
n-Heptyl chloride	—	160·0	20	0·8759	1·4255	39·33	26·9	349·9	0·956
			25	0·8715	—	—	26·35	349·9	0·890
n-Octyl chloride	—	183·8	20	0·8735	1·4298	43·93	27·65	390·1	1·23
			25	0·8695	—	—	27·15	390·1	1·135
sec.-Octyl chloride	—	171·9	20	0·8660	1·4283	44·17	26·4	388·9	1·055
			25	0·8616	—	—	25·9	389·1	0·973
n-Hexadecyl chloride	α 7·4°	195	20	0·8649	1·4495	80·93	31·1	711·8	6·34
	β 12·1	(22·5 mm.)	25	0·8616	—	—	30·6	711·7	5·51
Allyl chloride	—	45·0	20	0·9349	1·4165	20·56	23·7	180·5	0·347
			25	0·9290	—	—	23·1	180·5	0·331
Chlorobenzene	—	131·3	20	1·1065	1·5246	31·14	33·25	244·1	0·801
			25	1·1013	—	—	32·65	244·1	0·756
Benzyl chloride	—	67	20	1·0993	1·5391	36·06	37·65	285·1	1·40
		(14 mm.)	25	1·0945	—	—	36·95	285·0	1·29
Ethyl bromide	—	38·2	20	1·4612	1·4242	19·04	24·1	165·2	0·397
			25	1·4515	—	—	23·45	165·2	0·379
*iso*Propyl bromide	—	59·4	20	1·3096	1·4251	24·02	23·1	205·9	0·487
			25	1·3017	—	—	22·5	205·9	0·463
n-Butyl bromide	—	101·5	20	1·2758	1·4397	28·28	26·6	243·9	0·633
			25	1·2687	—	—	26·0	243·8	0·597
*iso*Butyl bromide	—	91·1	20	1·2641	1·4362	28·34	24·75	241·5	0·637
			25	1·2568	—	—	24·1	241·7	0·601
n-Amyl bromide	—	129·4	20	1·2190	1·4443	32·93	27·35	283·3	0·803
			25	1·2132	—	—	26·8	283·2	0·753
n-Hexyl bromide	—	154·6	20	1·1746	1·4475	37·57	28·2	323·7	1·013
			25	1·1691	—	—	27·65	323·7	0·941
n-Heptyl bromide	—	69·5	20	1·1406	1·4498	42·16	28·6	363·0	1·29
		(17 mm.)	25	1·1352	—	—	28·1	363·1	1·19
n-Octyl bromide	—	202·2	20	1·1126	1·4526	46·86	29·1	403·0	1·64
			25	1·1077	—	—	28·6	403·0	1·50
n-Hexadecyl bromide	16·3	190	20	0·9992	1·4614	83·87	31·8	725·3	7·81
		(11 mm.)	25	0·9952	—	—	31·4	725·3	6·75
Ethyl iodide	—	72·3	20	1·9364	1·5130	24·21	28·85	186·7	0·584
			25	1·9253	—	—	28·2	186·7	0·557
n-Propyl iodide	—	102·5	20	1·7478	1·5051	28·83	29·2	226·1	0·735
			25	1·7385	—	—	28·6	226·1	0·695
n-Butyl iodide	—	130·2	20	1·6150	1·4999	33·50	29·25	264·9	0·877
			25	1·6070	—	—	28·7	265·0	0·826
n-Hexyl iodide	—	76·5	20	1·4391	1·4926	42·79	30·25	345·5	1·39
		(23 mm.)	25	1·4326	—	—	29·75	345·7	1·285
n-Hexadecyl iodide	22·5	184	25	1·1220	1·4795	89·07	32·4	748·9	8·43
		(4 mm.)	30	1·1180	—	—	32·0	749·2	7·27
Methylene chloride	—	39·8	20	1·3283	1·4233	16·29	28·0	147·1	0·437
			25	1·3191	—	—	27·15	147·0	0·416
Chloroform	—	61·2	20	1·4892	1·4458	21·36	27·2	183·1	0·566
			25	1·4798	—	—	26·55	183·2	0·538
Carbon tetrachloride	—	76·75	20	1·5942	1·4603	26·47	26·75	219·5	0·968
			25	1·5846	—	—	26·15	219·6	0·902
1 : 2-Dichloroethane	—	83·6	20	1·2527	1·4448	21·02	32·45	188·5	0·829
			25	1·2454	—	—	31·75	188·6	0·775

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	*t*.	d_4^t.	n_D.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
1 : 3-Dichloropropane	—	120·8°	20°	1·1859	1·4483	25·52	33·8	229·7	1·034
			25	1·1800	—	—	33·05	229·6	0·963
1 : 4-Dichlorobutane	—	155·0	20	1·1408	1·4549	30·20	34·8	270·4	1·43
			25	1·1353	—	—	34·05	270·2	1·315
1 : 5-Dichloropentane	—	182·0	20	1·1006	1·4566	34·87	35·3	312·3	1·815
			25	1·0956	—	—	34·6	312·1	1·655
Ethylidene dichloride	—	57·3	20	1·1757	1·4167	21·15	24·75	187·7	0·490
			25	1·1680	—	—	24·1	187·7	0·465
1 : 1 : 2-Trichloroethane	—	114·1	20	1·4424	1·4715	25·87	33·75	222·9	1·19
			25	1·4355	—	—	33·0	222·7	1·10
1 : 1 : 2 : 2-Tetrachloroethane	—	146·1	20	1·5953	1·4940	30·62	35·6	256·9	1·765
			25	1·5876	—	—	34·9	256·9	1·615
1 : 1 : 1 : 2 : 2-Pentachloroethane	—	160·5	20	1·6813	1·5030	35·57	34·55	291·7	2·58
			25	1·6740	—	—	33·85	291·5	2·23
1 : 2 : 3-Trichloropropane	—	156·0	20	1·3880	1·4834	30·35	37·8	263·3	2·505
			25	1·3818	—	—	37·05	263·2	2·23
1 : 2-Dichloroethylene, *cis*	—	48·4	20	1·2583	—	—	26·4	174·6	0·423
			25	1·2502	—	—	25·8	174·7	0·400
1 : 2-Dichloroethylene, *trans*	—	60·1	20	1·2841	—	—	28·3	174·1	0·474
			25	1·2771	—	—	27·65	174·0	0·451
Trichloroethylene	—	86·9	20	1·4642	1·4775	25·38	29·6	209·1	0·566
			25	1·4559	—	—	28·8	209·1	0·532
Perchloroethylene	—	121·2	20	1·6230	1·5055	30·33	32·1	243·2	0·891
			25	1·6145	—	—	31·4	243·2	0·842
1 : 2-Dibromoethane	—	131·1	20	2·1802	1·5385	26·98	38·85	215·1	1·73
			25	2·1700	—	—	38·2	215·2	1·60
1 : 3-Dibromopropane	—	166·2	20	1·9812	1·5230	31·13	40·1	256·4	2·07
			25	1·9727	—	—	39·4	256·4	1·90
Ethyl *n*-butyl ether	—	92·0	20	0·7495	1·3820	31·71	20·75	290·8	0·421
			25	0·7448	—	—	20·25	290·8	0·397
Ethyl *n*-hexadecyl ether	19·9°	195 (21 mm.)	20	0·8182	1·4394	86·96	29·4	769·3	6·12
			25	0·8150	—	—	28·95	769·3	5·25
Methyl 2-chloroethyl ether	—	90·3	20	1·0522	1·4108	22·30	29·25	208·9	0·633
			25	1·0461	—	—	28·5	208·7	0·591
2-Chlorodiethyl ether	—	108·4	20	0·9954	1·4118	27·12	27·45	249·6	0·730
			25	0·9894	—	—	26·9	249·8	0·677
1 : 2-Dichlorodiethyl ether	—	51 (27 mm.)	20	1·1670	1·4418	32·40	29·8	286·2	1·285
			25	1·1610	—	—	29·1	286·0	1·165
2 : 2'-Dichlorodiethyl ether	—	177·9	20	1·2192	1·4573	31·95	37·6	290·4	2·41
			25	1·2130	—	—	37·0	290·7	2·14
1 : 2 : 2-Trichlorodiethyl ether	—	62 (13 mm.)	20	1·3227	1·4648	37·07	32·8	321·0	2·46
			25	1·3155	—	—	32·2	321·3	2·18
1 : 2 : 2 : 2 : 2'-Pentachlorodiethyl ether	—	112·5 (12·5 mm.)	20	1·5733	1·5025	46·25	38·9	391·1	9·36
			25	1·5669	—	—	38·3	391·0	7·83
Ethyl formate	—	54·3	20	0·9237	1·3599	17·69	23·8	177·1	0·402
			25	0·9173	—	—	23·15	177·1	0·382
Ethyl acetate	—	77·15	20	0·9007	1·3728	22·26	23·95	216·3	0·452
			25	0·8946	—	—	23·3	216·3	0·425
Ethyl butyrate	—	121·4	20	0·8794	1·3922	31·45	24·6	294·1	0·672
			25	0·8742	—	—	24·0	294·0	0·627
Ethyl valerate	—	145·1	20	0·8750	1·4005	36·09	25·4	333·8	0·821
			25	0·8703	—	—	24·85	333·8	0·763
Ethyl hexoate	—	167·0	20	0·8717	1·4072	40·72	26·0	373·4	1·024
			25	0·8672	—	—	25·45	373·3	0·948
Ethyl octoate	—	207·0	20	0·8676	1·4180	50·01	27·2	453·2	1·58
			25	0·8635	—	—	26·75	453·4	1·44

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	*t*.	d_4^t.	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
Ethyl nonoate	—	119°	20°	0·8661	1·4219	54·61	27·8	493·6	1·95
		(23 mm.)	25	0·8621	—	—	27·35	493·8	1·77
Ethyl laurate	−3·4°	273	20	0·8628	1·4310	68·47	29·05	614·1	3·36
			25	0·8591	—	—	28·6	614·3	2·99
Ethyl myristate	10·85	308·8	20	0·8616	1·4363	77·80	29·9	695·5	4·97
			25	0·8581	—	—	29·45	695·7	4·36
Ethyl palmitate	α 19·2	198·5	25	0·8568	1·4380	87·10	29·95	776·2	5·78
	β 23·2	(13·5 mm.)	30	0·8535	—	—	29·5	776·2	5·08
Ethyl margarate	α 25·2	200	30	0·8517	1·4380	91·94	29·65	817·3	5·815
	Tr↓ 11·5	(10 mm.)	35	0·8484	—	—	29·2	817·3	5·095
Methyl acetate	—	56·9	20	0·9342	1·3614	17·56	24·8	176·9	0·385
			25	0·9279	—	—	24·1	176·8	0·364
n-Propyl acetate	—	101·6	20	0·8874	1·3844	26·92	24·6	256·2	0·585
			25	0·8822	—	—	24·0	256·2	0·551
n-Butyl acetate	—	125·6	20	0·8796	1·3942	31·58	25·2	295·7	0·734
			25	0·8746	—	—	24·6	295·7	0·688
*iso*Butyl acetate	—	117·1	20	0·8745	1·3898	31·45	23·7	292·9	0·697
			25	0·8695	—	—	23·15	292·9	0·651
n-Amyl acetate	—	149·2	20	0·8753	1·4028	36·26	25·8	335·1	0·924
			25	0·8707	—	—	25·28	335·1	0·862
n-Hexyl acetate	—	170·5	20	0·8726	1·4096	40·89	26·55	374·9	1·17
			25	0·8681	—	—	26·0	374·9	1·075
n-Octyl acetate	—	211·5	20	0·8681	1·4193	50·11	27·8	455·5	1·85
			25	0·8638	—	—	27·3	455·7	1·68
n-Hexadecyl acetate	α 18·5	204	20	0·8611	1·4408	87·14	30·95	778·7	8·05
	β 22·1	(18 mm.)	25	0·8577	—	—	30·5	778·9	6·75
Ethyl malonate	—	199·3	20	1·0547	1·4139	37·93	31·9	360·8	2·15
			25	1·0494	—	—	31·3	360·8	1·94
Ethyl succinate	—	216·6	20	1·0402	1·4200	42·33	31·9	397·8	2·81
			25	1·0353	—	—	31·3	397·8	2·48
Ethyl adipate	−22	251	20	1·0076	1·4272	51·53	32·5	479·0	3·50
			25	1·0034	—	—	32·0	479·0	3·08
Ethyl suberate	—	283	20	0·9827	1·4325	60·81	32·75	560·3	4·74
			25	0·9783	—	—	32·2	560·5	4·17
Ethyl azelate	−19·8	172	20	0·9732	1·4344	65·40	32·85	600·7	5·32
		(18 mm.)	25	0·9692	—	—	32·35	600·9	4·65
Ethyl sebacate	+1·65	184	20	0·9631	1·4364	70·15	33·0	642·6	5·96
		(18 mm.)	25	0·9591	—	—	32·45	642·5	5·18
Ethyl ethylmalonate	—	208·2	20	1·0082	1·4164	46·86	29·8	436·0	2·41
			25	1·0037	—	—	29·1	435·4	2·15
Ethyl *n*-butylmalonate	—	239·0	20	0·9749	1·4226	56·42	29·1	515·0	3·47
			25	0·9703	—	—	28·55	515·0	3·02
Ethyl *n*-hexadecylmalonate	α 12·7	241	20	0·9118	1·4443	112·04	31·45	998·3	18·2
	β 25·1	(9·5 mm.)	23	0·9080	—	—	30·95	998·4	14·9
Ethyl benzoate	—	212·2	20	1·0468	1·5051	41·56	35·4	349·7	2·22
			25	1·0421	—	—	34·75	349·7	1·99
Ethyl chloroformate	—	92·6	20	1·1392	1·3952	22·84	26·1	215·3	0·557
			25	1·1325	—	—	25·45	215·2	0·528
Methyl chloroacetate	—	129·6	20	1·2345	1·4214	22·31	35·2	214·1	1·143
			25	1·2281	—	—	34·5	214·1	1·048
Ethyl chloroacetate	—	143·1	20	1·1510	1·4212	27·00	32·0	253·2	1·194
			25	1·1446	—	—	31·35	253·3	1·096
n-Propyl chloroacetate	—	162·9	20	1·1038	1·4253	31·65	30·95	291·7	1·50
			25	1·0977	—	—	30·35	291·9	1·365
n-Butyl chloroacetate	—	181·7	20	1·0707	1·4291	36·26	30·4	330·2	1·71
			25	1·0652	—	—	29·8	330·2	1·55

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	*t.*	d_4^t	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
Methyl dichloroacetate	—	143·9°	20°	1·3786	1·4424	27·46	34·0	250·4	1·546
			25	1·3712	—	—	33·25	250·4	1·414
Ethyl dichloroacetate	—	157·3	20	1·2804	1·4375	32·15	31·35	290·1	1·60
			25	1·2734	—	—	30·75	290·3	1·46
n-Propyl dichloroacetate		175·7	20	1·2234	1·4402	36·85	30·65	328·9	1·91
			25	1·2171	—	—	30·1	329·1	1·74
n-Butyl dichloroacetate	—	194·8	20	1·1841	1·4420	41·34	30·1	366·0	2·20
			25	1·1783	—	—	29·5	365·9	1·98
Methyl trichloroacetate	—	153·4	20	1·4870	1·4565	32·46	33·0	286·0	1·85
			25	1·4800	—	—	32·3	285·8	1·69
Ethyl trichloroacetate	—	167·3	20	1·3841	1·4501	37·17	30·8	325·8	1·72
			25	1·3773	—	—	30·2	325·8	1·57
n-Propyl trichloroacetate	—	185·5	20	1·3187	1·4507	41·93	30·6	366·4	2·04
			25	1·3123	—	—	30·05	366·5	1·86
n-Butyl trichloroacetate	—	206·0	20	1·2736	1·4514	46·43	30·55	405·1	2·38
			25	1·2674	—	—	30·0	405·2	2·14
2-Chloroethyl acetate	—	145·1	20	1·1556	1·4230	27·02	33·6	255·3	1·61
			25	1·1492	—	—	32·9	255·5	1·46
2-Chloroethyl chloroacetate	—	202·7	20	1·3584	1·4624	31·79	41·5	293·3	4·27
			25	1·3520	—	—	40·8	293·4	3·73
2-Chloroethyl dichloroacetate	—	213·0	20	1·4570	1·4738	36·91	39·8	330·0	5·09
			25	1·4504	—	—	39·1	330·0	4·41
2-Chloroethyl trichloroacetate	—	217·5	20	1·5329	1·4805	41·90	37·3	364·1	5·43
			25	1·5262	—	—	36·6	364·0	4·70
Ethyl β-chloropropionate	—	162·4	20	1·1044	1·4253	31·63	31·65	293·2	1·625
			25	1·0994	—	—	31·1	293·3	1·48
Diethyl sulphide	—	92·1	20	0·8367	1·4425	28·47	25·3	241·6	0·446
			25	0·8316	—	—	24·7	241·6	0·422
Di-*n*-butyl sulphide	—	188·1	20	0·8388	1·4525	47·07	27·35	398·6	1·072
			25	0·8348	—	—	26·8	398·5	0·995
Diisobutyl sulphide	—	170·0	20	0·8285	1·4471	47·16	25·1	395·0	0·944
			25	0·8244	—	—	24·6	395·0	0·880
Diisoamyl sulphide	—	215·3	20	0·8341	1·4531	56·48	26·3	473·0	1·525
			25	0·8303	—	—	25·85	473·2	1·395
2-Chlorodiethyl sulphide	—	59 (20 mm.)	20	1·0758	1·4898	33·47	33·1	277·8	—
2 : 2′-Dichlorodiethyl sulphide	14·4°	107 (15 mm.)	20	1·2746	1·5270	38·36	42·7	319·0	4·3
2-Chloroethyl 1 : 2-dichlorovinyl sulphide	—	107 (15 mm.)	20	1·4315	1·5562	43·01	40·9	338·3	2·8
2-Chloroethyl 1 : 2 : 2-trichlorovinyl sulphide	—	123 (15 mm.)	20	1·5425	1·5700	48·06	41·7	372·3	3·9
1 : 1 : 2-Trichloroethyl 2-chlorovinyl sulphide	—	122·5 (15 mm.)	20	1·5404	1·5661	47·85	41·7	372·8	5·7
1 : 2 : 2-Trichloroethyl 1 : 2-dichlorovinyl sulphide	—	134·5 (15 mm.)	20	1·6293	1·5778	53·02	41·8	406·2	6·5
1 : 1 : 2 : 2 : 2 : 2′-Hexachlorodiethyl sulphide	—	158·5 (15 mm.)	20	1·6849	1·5683	57·66	43·45	452·6	25·4
1 : 1 : 1′ : 2 : 2′ : 2′-Hexachlorodiethyl sulphide	—	159·5 (15 mm.)	20	1·6841	1·5681	57·68	43·35	452·5	29·4
1 : 1 : 1′ : 2 : 2 : 2′ : 2′-Heptachlorodiethyl sulphide	—	171 (15 mm.)	20	1·7473	1·5741	62·58	43·2	486·1	42·7
n-Butyl cyanide	—	141	20	0·7993	1·3975	25·06	27·6	238·3	0·753
			25	0·7952	—	—	27·1	238·4	0·705
n-Hexadecyl cyanide	31·7	195 (8 mm.)	30	0·8284	1·4431	80·44	31·35	717·8	7·65
			35	0·8254	—	—	30·85	717·5	6·55

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	*t*.	d_4^t.	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
n-Amylamine	—	105·3°	20°	0·7561	1·4115	28·65	23·15	258·1	0·720
			25	0·7519	—	—	24·65	258·3	0·658
n-Propyl alcohol	—	97·2	20	0·8053	1·3862	17·53	23·9	165·0	2·29
			25	0·8016	—	—	23·5	165·0	2·015
n-Butyl alcohol	—	117·9	20	0·8102	1·3992	22·13	24·8	204·1	2·98
			25	0·8066	—	—	24·35	204·1	2·60
*iso*Butyl alcohol	—	108·0	20	0·8030	1·3953	22·13	23·0	202·0	3·82
			25	0·7994	—	—	22·55	201·9	3·24
n-Amyl alcohol	—	137·5	20	0·8146	1·4103	26·81	25·6	243·2	3·65
			25	0·8110	—	—	25·15	243·3	3·19
n-Hexyl alcohol	—	156·6	20	0·8198	1·4174	31·35	26·55	282·8	5·32
			25	0·8164	—	—	26·05	282·7	4·52
n-Heptyl alcohol	—	175·9	20	0·8236	1·4236	35·96	27·25	322·2	7·60
			25	0·8202	—	—	26·75	322·0	6·87
n-Octyl alcohol	—	194·6	20	0·8265	1·4287	40·57	27·9	361·7	9·13
			25	0·8232	—	—	27·4	361·9	7·55
n-Butyric acid	—	163·4	20	0·9585	1·3981	22·18	26·8	209·6	1·72
			25	0·9537	—	—	26·2	208·9	1·57
n-Valeric acid	—	185·6	20	0·9386	1·4085	26·86	27·4	248·8	2·25
			25	0·9342	—	—	26·85	248·7	2·03
n-Hexoic acid	—	205·3	20	0·9271	1·4162	31·44	28·05	288·2	3·22
			25	0·9230	—	—	27·55	288·2	2·87
n-Octoic acid	15·9°	237·7	20	0·9110	1·4279	40·70	29·2	367·8	6·09
			25	0·9070	—	—	28·7	367·8	5·29
n-Nonoic acid	12·0	254·0	20	0·9052	1·4322	45·33	29·7	407·9	8·30
			25	0·9013	—	—	29·2	407·9	7·15

DISCUSSION.

The results obtained, given in the accompanying table, agree in general with those of other workers, and in particular with the recent data of Timmermans and his collaborators (*J. Chim. physique*, 1926, **23**, 747; 1928, **25**, 411; 1930, **27**, 401; 1932, **29**, 529; 1934, **31**, 85; 1935, **32**, 501, 589; 1937, **34**, 693; cf. Roland and Lek, *Bull. Soc. chim. Belg.*, 1931, **40**, 177) and of Vogel (*J.*, 1934, 333; 1943, 16, 637; 1946, 133; 1948, 607 *et seq.*, 1804 *et seq.*).

The only marked discrepancies occur with the surface tensions of the C_6—C_8 alcohols, and one or two other liquids of high viscosity, where the capillary rise method used by these workers appears to give low and erratic results. The discontinuity in surface tension at C_7 in the alcohol series noted by Smith and Sorg (*J. Physical Chem.*, 1941, **45**, 671) has not been confirmed.

In view of the incompleteness of the investigation, and of the recent extensive work of Vogel in the same field, little useful purpose would be served by detailed analysis of the results now reported. A few points, however, merit brief discussion.

First, as regards the CH_2 parachor increment: The present measurements of parachor increase from C_4 to C_{10} in nine different aliphatic series support a mean increment of 40 units originally advocated in our earlier paper and now accepted by Vogel on the basis of his own data. It must, however, be appreciated that this is a representative average value, and that owing to slight variation of the exponent in the Kleeman–MacLeod relation, $\gamma = C(D - d)^4$, from compound to compound, the observed increment in any given case depends both on the temperature range of measurement, and on the particular series being examined and the number of terms considered. The parachor is, in fact, not strictly a constant, and only approximately homologously additive.

The atomic and group constants previously evaluated on the basis of this increment reproduce satisfactorily the parachor data now reported, and would not therefore appear to require significant modification. Such constants are, not unnaturally, much the same as those recently put forward by Vogel on the same basis, as will be seen from the subjoined tabular summary of the more important values.

Atom or Group.	*P* value. M. & P.	V.	Atom or Group.	*P* value. M. & P.	V.
CH_3	40	40·0	Cl	55	55·2
H in CH_3	15·4	15·7	Br	69	68·8
C in CH_3	9·2	8·6	I	90	90·3
CH_2	55·4	55·4	CN	64·7	64·6
C_2H_3	95·4	95·4	O in ethers	20	19·8
Allyl	123·6	124·3	S in sulphides	50	48·6
Phenyl	190	188·3	CO_2 in esters	65·2	63·4
Double bond	19	19·9	OH in alcohols	30	30·2
6-Ring	0·8	1·4	CO_2H	73·2	73·7

M. & P. = Mumford and Phillips *J.*, 1929, 2112 (Table I).
V. = Vogel, *J.*, 1948, 1833 (Table XXII).

In the case of many atoms and groups (*e.g.*, halogen, ethereal oxygen, cyanogen, etc.) the two sets of constants are indeed virtually identical, though with certain of the more complex groupings (*e.g.*, phenyl, CO·O in esters) they differ by one or more units. Vogel's values are based on much more extensive data, but any resulting gain in accuracy would appear to be largely offset by the circumstance that each group value has been independently evaluated, and cannot be quantitatively computed by summation of its component atomic and structural constants. This applies, rather illogically, to the lower alkyl groups themselves in Vogel's system, in which the successive CH_2 differences from methyl to octyl are given as 40, 39·9, 39·8, 39·7, 40, 40·7, and 40, respectively, one curious result of this being that the calculated parachor of, say, *n*-hexane, varies according to whether it is considered as *n*-hexyl + H (270·7), *n*-amyl + methyl (270·4), *n*-butyl + ethyl (270·7), di-*n*-propyl (271·0), $4CH_2 + 2$ methyl (270·8), or $6CH_2 + 2H$ (271·4).

The decrement of 3 units previously noted as applying to branched-chain groups of the type $-CHR_2$ receives support from the parachors of the few *iso*-compounds now reported, and it is interesting to note in this connection that according to Vogel the parachor values of *iso*- and *sec.*-alkyl groups range from 1·5 (*iso*butyl) to 4·1 (*sec.*-butyl) units lower than those of the corresponding *n*-groups.

The well-defined parachor defect associated with accumulation of negative atoms and groups (X) around a central carbon atom would appear to depend to a rather greater extent than was originally surmised on the size and polarity of the atoms and groups concerned, but the parachors now reported, and other recently recorded data, confirm in general the earlier conclusion that for X = Cl, OEt, CO_2Et, and for similar groups the decrement (" strain constant ") associated with $-CHX_2$ groups may be taken as 3 units, with $-CX_3$ groups 6 units, and with compounds of the type CX_4 9 units, within the limits of experimental error; and further, that for such atoms and groups the more complex effect of accumulation on adjacent carbon atoms can be adequately estimated in the manner previously outlined. The depressive effect of negative accumulation on the parachor has been recognised by Vogel in his latest paper (*loc. cit.*), but qualitatively only, and apparently without full appreciation of its applicability, for example, to esters $-C<^{O-}_{O}$ as in acetals $-CH<^{O-}_{O-}$, and of its occurrence to a varying extent in the chlorides and oxychlorides of phosphorus and sulphur, and in many of the esters of the inorganic acids (cf. Table VIII in our original paper).

The general validity of parachors calculated in accordance with the scheme outlined in that table has received additional support from the measurements of Pearson and Robinson (*J.*, 1933, 1427) on sulphur hexafluoride, and of Denbigh and Whytlaw-Grey (*J.*, 1934, 1346) on disulphur decafluoride. In both cases, allowing a " strain constant," due to accumulation, of −15 units per S^{VI} atom, and assuming that the valencies of the latter comprise two co-valent bonds and four " singlet " linkages, the values obtained for the latter linkage (−11·2 and −11·1, respectively) agree closely with similar values derived from other compounds, *e.g.*, tellurium tetrachloride (−11·4; Simons, *J. Amer. Chem. Soc.*, 1930, **52**, 3488; with Te = 79) and phosphorus pentachloride (−10·5; Sugden, *J.*, 1927, 1173). The " strain constant " would here appear to connote the screening effect of the surrounding halogens on the central atom, and to be distinct from the defect attributed, following Sugden, to " singlet " linkages, which is presumably connected with the formation of bonds involving inner electron orbits.

The need for assuming the presence of such linkages in compounds of this type, and of semi-polar double (" dative ") bonds in the corresponding oxyhalides and esters, can to some extent be avoided by assigning different parachor values to the central atom in its different valency

states (cf. previous paper, p. 2125; also Sippel, *Ber.*, 1930, **63**, *B*, 2185; Buehler, *J. Tennessee Acad. Sci.*, 1931, **6**, 27; Hunter and Samuel, *Rec. Trav. chim.*, 1935, **54**, 114). This procedure, however, does not eliminate the depressive effect of accumulation, and moreover leads to inconsistent and improbable atomic values for the elements concerned in their higher valencies. Thus, according to Samuel (*J. Chem. Physics*, 1944, **12**, 167) the atomic parachor of P^{v} is 18·3 in $POCl_3$, though only 11·0 in PCl_5, whilst that for S^{vi}, given as +13·9 in SO_2Cl_2, is, on the same basis (using Sugden's value of 25 for F), −6·7 in SF_6. So far as concerns the "dative" bond, Vogel's conclusion that parachor data provide no evidence for the presence of co-valent double bonds in the esters and oxyhalides of sulphur and phosphorus, as maintained by G. M. Phillips, Hunter, and Sutton (*J.*, 1945, 146), would appear to be well-founded (cf. Wells, *J.*, 1949, 55).

The view previously advanced, that the effective parachor value of the hydrogen atom depends inversely on the electron affinity of the atom to which it is attached, has been discussed in some detail by Pearson and Robinson (*J.*, 1934, 736) and supported and extended by their measurements of the parachors of the non-metallic hydrides (*J.*, 1932, 972; 1934, 730, 880). Confirmation of the lower parachor value of H in OH groups has also been afforded by Vogel for alcohols and acids (*J.*, 1948, 1814), though attributed by him to variation in the parachor of the oxygen atom.

In the light of modern views on structure, a number of the interpretations of deviations from parachor additivity suggested in our previous paper require some modification, and the atomic and structural constants then put forward could doubtless be more precisely evaluated with the aid of the very considerable additional data now available. Taking the system as originally advanced twenty years ago, however, it may be noted that, of the 690 parachor values recorded by Vogel since Part I of his present series (*J.*, 1934, 333), the difference between calculated (Mumford and Phillips) and observed parachors exceeds 2% in only 23 instances (*i.e.*, 3% of the total), whilst for over 80% of the compounds the agreement is within 1%.

Direct comparison with Vogel's system is not possible for the whole of this series, as his method of computation is not at present applicable to many of the complex esters, etc., considered in his earlier papers. Of more than six hundred compounds listed since Part VII of the series (*J.*, 1943, 16), however, only 63 are not computable by the atomic and group constants given by Vogel in his latest paper, these including, *inter alia*, *tert.*-butyl and amyl compounds, naphthalene derivatives, acetylenedicarboxylic esters, aromatic *tert.*-amines, and a variety of polyhalogenated compounds. Exclusion of these, and the few compounds for which surface tension data are not given, leaves 527 compounds of a wide variety of types, whose parachors can be evaluated by both systems; when this is done, the following comparative analysis of results is obtained.

System of evaluation.	Percentage of compounds for which the difference between calc. and obs. parachors is Within 0·5%.	Within 1%.	Above 2%.
Vogel's data (527 compounds).			
Vogel	67·8	88·7	2·1
Mumford and Phillips	52·9	85·5	1·7

It will be seen that the overall agreement is not very different in the two cases, although Vogel's system gives somewhat closer reproducibility with a greater number of compounds. This is not surprising in view of the circumstance that his constants were derived exclusively from the data to which they are now applied. In the following table a similar comparison is made with parachor data from the measurements of Timmermans and his collaborators (*loc. cit.*) and from the determinations reported in this paper, excluding in both instances such multi-branched and polyhalogenated compounds as cannot at present be evaluated by Vogel's system.

System of evaluation.	Percentage of compounds for which the difference between calc. and obs. parachors is Within 0·5%.	Within 1%.	Above 2%.
Timmerman's data (126 compounds).			
Vogel	54·8	79·4	5·5
Mumford and Phillips	54·0	86·5	3·2
Data from present paper (102 compounds).			
Vogel	63·7	89·2	3·0
Mumford and Phillips	63·7	96·0	1·0

The position is here somewhat different, the values calculated according to Vogel showing the smaller overall agreement. It would seem, therefore, that the employment of a multiplicity

of independently evaluated and unrelated group constants is a refinement which over-estimates the precision of the parachor, and that there is much to be said for adhering to the scheme advocated in our original paper.

Part of this work was carried out at a Ministry of Supply Establishment, and the authors thank the Chief Scientist of the Ministry for permission to publish the data so obtained.

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20. *The Enzymic Synthesis and Degradation of Starch. Part VI. The Properties of Purified P- and Q-Enzymes.*

By S. A. BARKER, E. J. BOURNE, I. A. WILKINSON, and S. PEAT.

Directions are given for the preparation of the phosphorylase (P-enzyme) and the cross-linking enzyme (Q-enzyme) of potato as stable, freeze-dried powders. The freeze-drying must be carried out in a citrate buffer of pH 6—7, otherwise both enzymes are destroyed.

The purified P-enzyme (fraction P2) contained no maltase and only traces of Q-enzyme or the normal amylases. It showed a slight phosphatase activity on glycerophosphate but not on glucose-1 phosphate.

The purified Q-enzyme (fraction Q3) was substantially free from maltase, the amylases, and phosphatase. It contained a little P-enzyme, equivalent to 5% of that in the original juice.

Fraction P2 has *per se* no effect on the viscosity of starch paste. Q-Enzyme, on the other hand, has a striking liquefying action, in the presence or absence of phosphate.

Q-Enzyme has a strong accelerating effect on the rate of synthesis of polysaccharide from glucose-1 phosphate by P-enzyme. Q-Enzyme is irreversibly inactivated by being precipitated from aqueous solution by acetone.

The conversion of amylose into amylopectin by Q-enzyme is not inhibited by phloridzin. Moreover, the synthetic activity of P-enzyme is only slightly inhibited by phloridzin.

The significance of these observations is discussed in the succeeding paper (Part VII).

THE study of the extraction and the properties of the cross-linking (Q-) enzyme of potato, described in Part IV of this series (Barker, Bourne, and Peat, *J.*, 1949, 1705), has been continued and extended to include the potato-phosphorylase (P-enzyme) which is separated in the same process. The method of isolation of the two enzymes is diagrammatically represented in Table I.

It was reported in Part IV that precipitates of Q-enzyme could be freeze-dried with little loss of activity if, to the moist precipitate, boiled potato juice were added before it was submitted to freeze-drying. It seemed probable that the boiled juice was simply buffering the enzyme slurry which, in its absence, became acid owing to loss of ammonia from ammonium sulphate. We have now been able to confirm this supposition and to show by the use of suitable buffers that P-enzyme preparations may also be freeze-dried without loss of activity.

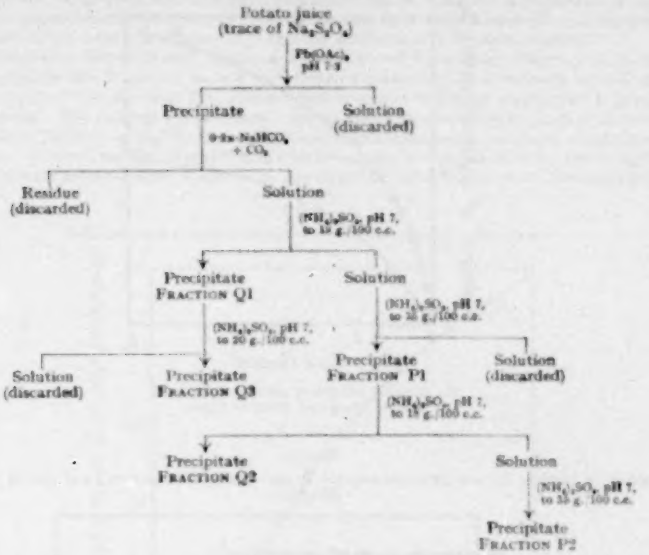
P-Enzyme.—The synthetic activity of fraction P2 (Table I) was completely destroyed by freeze-drying, whereas the less pure fraction, P1, retained about 25% of its activity. During the freeze-drying of the latter fraction the pH fell from 7·3 to *ca.* 5·5 (Table II). Boiled and filtered potato juice stabilised both fractions to freezing and the maximum acidity change was, in this case, from pH 7·2 to 6·4 (Table III). The effect of freeze-drying P1 (and P2) fractions in the presence of different buffers is shown in Tables IV and V. It was concluded that complete retention of the activity of P-enzyme was possible if the freeze-drying was carried out in a 0·2M-citrate buffer of pH 6·0.

Q-Enzyme.—It is shown in Table VI that the activity of Q-enzyme (in the conversion of amylose into amylopectin) is completely retained if a Q3 fraction (see Table I) is freeze-dried in a 0·2M-citrate buffer of pH 6·0, 6·5, or 7·0, and for routine preparations we have adopted the procedure of freeze-drying in such a citrate buffer at pH 7·0. It is a matter of considerable interest that, although a citrate buffer of pH 7·0 allows of maximum retention of Q-activity, yet an acetate buffer of the same pH is quite ineffective. In fact, a Q3 preparation freeze-dried in an acetate buffer of pH 7·0 was almost completely inactivated (Table VI). This loss of activity appears to be associated with the development of acidity during the drying process. The final pH with acetate was 5·15, as compared with 6·5 when citrate was used. Table IV indicates that P-enzyme also is destroyed by freeze-drying in an acetate buffer of pH 7·0.

Stocks of fractions P2 and Q3 were prepared from more than 60 kg. of potatoes during the "resting" stage, *i.e.*, when the amylase content was a minimum, and were freeze-dried in citrate buffers of pH 6·0 and 7·0, respectively. The dry powders were stable during prolonged periods; for instance, the dried fraction P2 lost not more than 1% of its activity in 60 days,

TABLE I.

Isolation of P- and Q-enzymes from potato juice.



whereas the activity of the same sample kept in solution in citrate buffer (pH 6·0) for the same time fell to one-tenth of its initial value. The Q3 powder showed no change in Q-enzyme activity in 41 days.

The Enzymic Purity of Fractions P2 and Q3.—The Q3 fraction was shown in Part IV to be substantially free from the normal amylases and from maltase. It contained a little P-enzyme (detected by its synthetic activity) corresponding, after freeze-drying, to about 5% of the P-enzyme initially present in the juice. The P2 fraction was also shown to be free from maltase (lack of maltose-hydrolysing activity). It contained, at most, only traces of Q-enzyme and the normal amylases inasmuch as it effected, at pH 6—7, only a very slow fall in the A.V. (6800 A.) of amylose.

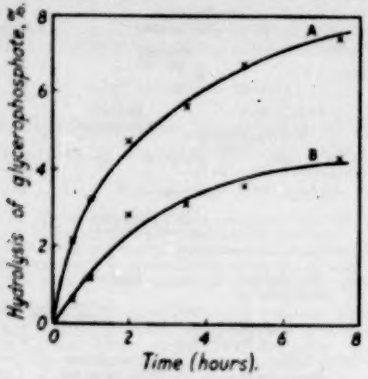
Phosphatase Content.—The Q3 fraction did not liberate a detectable amount of free phosphate from sodium glycerophosphate in 7·5 hours at pH 6·5 and might thus be considered as free from phosphatase. The freeze-dried P2 fraction did, however, contain a trace of phosphatase since it effected a 7·5% conversion of glycerophosphate into free phosphate in 7·5 hours (see Fig. 1, curve *A*). It appeared that this reaction was either reversible or was inhibited by phosphate ion since the hydrolysis of glycerophosphate proceeded much more slowly in the presence of added mineral phosphate (Fig. 1, curve B). Fraction P2 exerted no phosphatase activity with respect to glucose-1 phosphate under the normal conditions of polysaccharide synthesis. Thus, when fraction P2 was incubated at pH 6·0 in the presence of starch with glucose-1 phosphate no development of reducing power occurred in one hour.

Starch-liquefying Action of P- and Q-Enzymes.—The relative viscosity of a 1% dispersion of potato starch in acetate buffer (pH 7·0) was not affected by fraction P2. In a phosphate buffer of pH 6·7, a slow fall in the viscosity was observed (Fig. 2) and could be attributed to normal phosphorolysis of the starch.

It was reported in Part I (Bourne and Peat, *J.*, 1945, 877) that the crude preparations of the branching enzyme then available liquefied starch pastes. That this is an intrinsic action of Q-enzyme has now been demonstrated by the striking diminution of viscosity of a 1% starch paste brought about by the highly purified Q3 fraction (Fig. 2). As pointed out above,

FIG. 1.

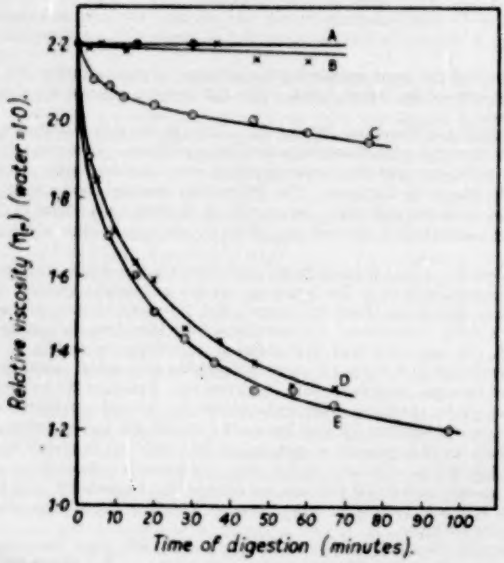
Phosphatase activity of enzyme fraction P2 *(sodium glycerophosphate substrate).*



A. Mineral phosphate not added to digest.
B. Mineral phosphate added to digest.

FIG. 2.

The action of fractions P2 *and* Q3 *on the viscosity of starch paste in the presence and absence of mineral phosphate.*



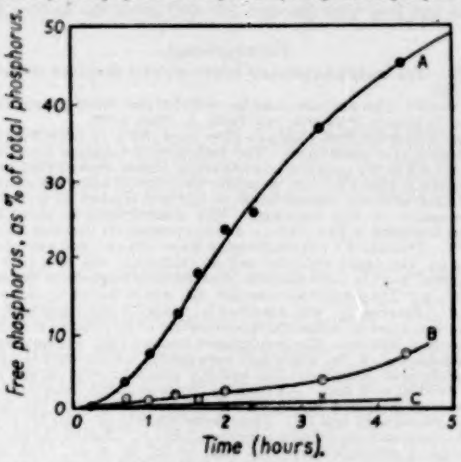
A. Water (acetate buffer).
B. P_3 *(Acetate buffer).*
C. P_3 *(Phosphate buffer).*
D. Q_3 *(Acetate buffer).*
E. Q_3 *(Phosphate buffer).*

there are reasons for believing that fraction Q3 does not contain α-amylase in sufficient concentration to cause this degree of liquefaction. Nor can the liquefaction be ascribed to phosphorolysis. It is true that a somewhat greater fall in viscosity is registered if mineral phosphate is present in the Q3 digest (Fig. 2), but we ascribe this enhanced effect in the presence of phosphate to the small proportion of P-enzyme which the Q3 fraction contains.

Autocatalysis in Polysaccharide Syntheses from Glucose-1 Phosphate.—The rate of liberation of free phosphate by P-enzyme acting on glucose-1 phosphate is a measure of the rate of synthesis of polysaccharide, and Fig. 3 shows that this rate is greatly accelerated if Q-enzyme is also present. The enzyme preparations used in this experiment were purified beyond the stages given in Table I, by two further precipitations with ammonium sulphate, giving fractions P4 and Q5. Curve *C* in Fig. 3 shows that the P-enzyme content of fraction Q5 is negligibly small. The autocatalytic effect is shown by the difference between curve *B* (P4 fraction alone)

FIG. 3.

Autocatalysis in polysaccharide synthesis from glucose-1 phosphate.



A. P-*Enzyme* + Q-*enzyme.*
B. P-*Enzyme alone.*
C. Q-*Enzyme alone.*

and curve *A* (P4 and Q5 acting together). Cori and Cori (*J. Biol. Chem.*, 1943, **151**, 57) showed that the " branching factor " of liver and heart had a similar catalytic effect on the synthetic action of muscle phosphorylase, and ascribed the effect to the increase in the proportion of non-reducing chain ends brought about by the branching factor. Clearly Q-enzyme functions in the same way. It has been indicated by Bernfeld and Meutémédian (*Helv. Chim. Acta*, 1948, **31**, 1724) that α-amylase, which fragments amylose chains, would, by increasing the number of chain ends, also catalyse the synthesis from glucose-1 phosphate (see also Part III, Bourne, Peat, and Sitch, this vol., p. 1448). This autocatalytic action cannot therefore be regarded as a specific test for Q-enzyme.

The Inactivation of Q-Enzyme by Acetone.—It was shown in Part II (Bourne, Macey, and Peat, *J.*, 1945, 882) that Q-enzyme was inactivated by precipitation from aqueous solution with ethyl alcohol (3 vols.) whereas salivary α-amylase was unaffected by alcohol. We have now found that the activity of the purified Q-enzyme (fraction Q3) is almost completely destroyed when it is precipitated from a citrate buffer solution at pH 6 and 0° with acetone at concentrations between 25 and 40%.

The Effect of Phloridzin on P- and Q-Enzymes.—Green and Stumpf (*J. Biol. Chem.*, 1942 **142**, 355) reported that potato phosphorylase was partly inhibited (in its synthetic action) by phloridzin. At a phloridzin concentration of (approx.) $1{\cdot}4 \times 10^{-3}$M., the inhibition was only

18%, and at half this concentration there was no inhibition of phosphorylase. Bernfeld and Meutémédian (*loc. cit.*, p. 1735) showed that isophosphorylase was not inhibited by phloridzin and, on the assumption that phosphorylase was strongly inhibited by phloridzin, added the latter reagent to mixtures of phosphorylase and isophosphorylase in order to influence the relative active concentrations of the two enzymes.

We have now examined the effect of phloridzin on the conversion of amylose into amylopectin by Q-enzyme and on the synthesis of amylose from glucose-1 phosphate by P-enzyme. Caution had to be observed when measuring the activity of fraction Q3 by diminution of A.V. (6800 Å.) for it was shown that phloridzin reacts rapidly with free iodine and also, but more slowly, changes the blue colour of an amylose–iodine complex. To overcome this difficulty when Q-enzyme was incubated with amylose in the presence of phloridzin, more than the standard concentration of iodine was employed and the absorption value was measured immediately after staining. By adopting this technique we were able to show that Q3 fraction was not inhibited at all by $1{\cdot}5 \times 10^{-3}$M-phloridzin (see Table VII).

Furthermore, we found that the introduction of phloridzin ($1{\cdot}24 \times 10^{-3}$M.) into a digest of glucose-1 phosphate and P-enzyme (fraction P2) diminished the enzyme activity by only 8% (Table VIII).

Experimental.

Analytical Methods.—The analytical methods employed were described in Part IV (Barker, Bourne, and Peat, *J.*, 1949, 1705).

Fractionation of Starch.—The amylose samples were isolated from potato starch by precipitation with thymol (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687).

Isolation of P- and Q-Enzymes from Potatoes.—The juice (100 c.c.) from King Edward potatoes was treated with lead acetate and centrifuged. The lead–protein complex was eluted by stirring with sodium hydrogen carbonate in the presence of a stream of carbon dioxide (details of these early stages of the isolation were given in Part IV). To the eluate (*ca.* 110 c.c.) ammonium sulphate solution (pH 7; 50 g./100 c.c.) was added until the concentration of this salt reached 18 g./100 c.c. The precipitate (fraction Q1) was separated by the centrifuge. The concentration of ammonium sulphate in the supernatant liquid was increased to 35 g./100 c.c. and the precipitate (fraction P1) was collected.

Fractionation of P1. Fraction P1 was dissolved in water (20 c.c.) and ammonium sulphate solution (pH 7·0; 50 g./100 c.c.) was added until the salt concentration was 18 g./100 c.c. The precipitate (fraction Q2) was removed and the concentration of ammonium sulphate in the supernatant liquid was increased to 35 g./100 c.c. The precipitate (fraction P2) was collected by the centrifuge.

Fractionation of Q1. Fraction Q1 was dissolved in water (20 c.c.) and kept at 0° for 1 hour. A small insoluble residue was removed before the concentration of ammonium sulphate in the solution was adjusted, as above, to 20 g./100 c.c. The precipitated fraction (Q3) was separated by the centrifuge.

Except where otherwise stated, the operations were carried out at room temperature.

Freeze-drying of P-Enzyme Solutions.—The enzyme solutions were frozen in an alcohol–carbon dioxide mixture and dried at 0·01 mm. No thawing occurred under these conditions. The activities of the enzyme samples were measured by the method of Green and Stumpf (*loc. cit.*).

(a) *Freeze-drying of fractions P1 and P2.* The enzyme fraction (P1 and P2) isolated from 100 c.c. of juice was dissolved in water, and the volume adjusted to 20 c.c. Half of the solution was freeze-dried, the powdery product being redissolved in water and diluted to 10 c.c. The other half served as a control. The results obtained with several different samples of P1 and P2 are given in Table II.

Table II.

Freeze-drying of fractions P1 and P2.

Enzyme fraction.	pH of enzyme solution: before drying.	pH of enzyme solution: after drying.	Retention of P-enzyme activity during freeze-drying (%).	Enzyme fraction.	pH of enzyme solution: before drying.	pH of enzyme solution: after drying.	Retention of P-enzyme activity during freeze-drying (%).
P1	7·20	5·65	45·7	P1	7·35	5·06	8·6
,,	7·34	5·65	15·8	,,	7·29	5·60	17·7
,,	7·36	5·51	42·6	P2	—	—	0·0
,,	7·24	5·71	35·0	,,	—	—	0·0

(b) *Freeze-drying of fractions P1 and P2 in the presence of boiled potato juice.* A sample of potato juice was boiled for 20 minutes, filtered, and diluted to its original volume with distilled water. To a solution (20 c.c.) of fraction P1 or P2, obtained from 100 c.c. of juice, 5 c.c. of the boiled juice were added and the enzyme solution thus obtained was divided into two equal portions. One of these was freeze-dried, the dry residue being redissolved in water and diluted to 12·5 c.c. The second half served as a control. It was essential that this control should contain boiled juice because, under these conditions, the addition of boiled juice to fraction P1 or P2 increased the activity of the phosphorylase solution by about 15%. The stabilising effect of boiled juice during the freeze-drying of P-enzyme solutions is shown in Table III.

(c) *Freeze-drying of fraction P1 in the presence of different buffers.* The boiled juice used in (b) was replaced by different buffer solutions as shown in the Table IV. It was observed that the mere addition of 0·2M-sodium hydrogen carbonate, even without freeze-drying, diminished the P-enzyme activity by about 30%.

TABLE III.

Freeze-drying of fractions P1 and P2 in the presence of boiled potato juice.

Enzyme fraction.	pH of enzyme solution, containing boiled juice: before drying.	after drying.	Retention of P-enzyme activity during freeze-drying (%).
P1	7·09	6·40	95·0
,,	7·26	6·40	100·0
P2	—	—	100·0

TABLE IV.

Freeze-drying of fraction P1 in the presence of different buffers.

Buffer solution.	Volume of buffer added to 20 c.c. of P1 solution (c.c.).	Retention of P-enzyme activity during freeze-drying (%).
0·1M-Citrate (pH 6·3)	4·0	66·8
0·1M-Glycine (pH 8·2)	,,	59·5
1·0M-Acetate (pH 7·0)	,,	0·0
0·2M-$NaHCO_3$	,,	47·2
,,	,,	53·0
,,	,,	51·8
0·8M-$NaHCO_3$	8·0	29·4
,,	,,	51·5

(d) *Freeze-drying of solutions of fractions P1 and P2 in 0·2M-citrate buffer (pH 6·0).* Fraction P1 (or P2), isolated from 100 c.c. of potato juice, was dissolved directly in 0·2M-citrate buffer (pH 6·0) to give 20 c.c. of enzyme solution, half of which served as a control. The other half was freeze-dried, the product being redissolved in water and diluted to 10 c.c. The efficacy of the citrate buffer as a stabiliser during the freeze-drying of P1 and P2 fractions is shown in Table V, where the results obtained with several different samples of these enzymes are recorded.

TABLE V.

Freeze-drying of solutions of fractions P1 and P2 in 0·2M-citrate buffer (pH 6·0).

Enzyme fraction	P1	P1	P1	P1	P2	P2
Retention of P-enzyme activity during freeze-drying (%)	100·0	98·5	100·0	100·0	100·0	100·0

In view of the above results, this method of freeze-drying fractions P1 and P2 in 0·2M-citrate buffer (pH 6·0; 20 c.c. for each 100 c.c. of juice originally used) was adopted as the standard method for the preparation of the enzymes in powder form, and has been successfully employed for the isolation and storage of the P-enzyme from more than 60 kg. of potatoes.

Freeze-drying of Fraction Q3 in the Presence of Citrate and Acetate Buffers.—Fraction Q3, isolated from 125 c.c. of juice, was dissolved in 0·2M-citrate buffer (pH 6·0; 25 c.c.). A portion (20 c.c.) of this solution was freeze-dried, as above, the rest being retained as a control. The dry powder was dissolved in water, diluted to 20 c.c., and incorporated in a digest consisting of amylose solution (14 mg. in 7·5 c.c., prepared as in Part IV), maltose solution (3·0 mg. in 1·5 c.c.), 0·2M-citrate buffer (pH 6·0; 3 c.c.), and the buffered enzyme solution (2·0 c.c.), making a total volume of 14·0 c.c. A second digest contained the enzyme control. After 30 minutes at 20·5° an aliquot portion (1·0 c.c.) of each digest was stained with iodine (2·0 mg.)–potassium iodide (20·0 mg.) in a final volume of 100 c.c. and the A.V. (6800 A.) was measured in the usual manner.

In three similar experiments the 0·2M-citrate buffer (pH 6·0) was replaced, both during freeze-drying and in the digests, by other buffers, namely, 0·2M-citrate buffer (pH 6·5), 0·2M-citrate buffer (pH 7·0), and 0·2M-acetate buffer (pH 7·0). The results are shown in Table VI.

TABLE VI.

Freeze-drying of solutions of fraction Q3 in acetate and citrate buffers.

Buffer used during freeze-drying and in the digests.	Fall (%) in A.V. (6800 A.) in 30 mins. Control.	After freeze-drying.	pH of enzyme-buffer solution after freeze-drying.
0·2M-Citrate (pH 6·0)	74·7	72·6	5·83
0·2M-Citrate (pH 6·5)	79·4	76·8	6·21
0·2M-Citrate (pH 7·0)	79·5	76·8	6·51
0·2M-Acetate (pH 7·0)	74·5	0·8	5·15

For routine purposes, the standard technique adopted for the freeze-drying of fraction Q3 was to dissolve the enzyme in 0·2M-citrate buffer (pH 7·0; 12·5 c.c. for each 100 c.c. of juice), freeze the solution in an alcohol–carbon dioxide mixture, and dry it at 0·01 mm. In this way a very active enzyme preparation has been obtained in powder form from more than 60 kg. of potatoes.

The Stability of Fractions P1 and P2 when stored at 0°.—Fraction P1 was dissolved in 0·2M-citrate buffer (pH 6·0; 20 c.c. for each 100 c.c. of juice originally employed) and the solution was divided into two parts. One of these was freeze-dried as above, the other being kept as a control. The solution and the dry powder were stored at 0° in tightly-stoppered bottles, and the P-enzyme activity of each was measured at intervals by the method of Green and Stumpf (*loc. cit.*). In a second experiment fraction P2 was used. The rates of decay in P-enzyme activity are shown below.

The stabilities of fractions P1 and P2 in citrate buffer (pH 6·0) at 0°.

Enzyme fraction.	Method of storage.	Retention of P-enzyme activity (%). 12 days.	27 days.	60 days.
P1	Solution	94·2	83·5	60·0
,,	Powder	100·0	99·0	98·0
P2	Solution	59·0	49·5	9·1
,,	Powder	100·0	100·0	99·0

The Stability of Fraction Q3 when stored at 0° as a Powder.—Fraction Q3 was dissolved in 0·2M-citrate buffer (pH 7·0) and freeze-dried according to the standard technique described above. The powder was stored at 0° in a well-stoppered bottle, samples being periodically removed and incubated with amylose in the manner already described. The figures quoted in the following table show that there was no detectable loss in Q-enzyme activity in 41 days.

The stability of fraction Q3 when stored at 0° in powder form.

Time of storage (days)	10	27	41
Fall (%) in A.V. (60·0 A.) of amylose in 30 mins.	75·0	75·2	75·1

Tests for Phosphatase in Fractions P2 and Q3.—The enzyme fractions (P2 and Q3) used in these tests had been stored for several weeks as the dry powders obtained when their solutions in 0·2M-citrate buffers were freeze-dried under the standard conditions already described.

(a) *With sodium glycerophosphate as substrate for fraction P2.* The solutions used were 0·1M-sodium glycerophosphate in 0·2M-citrate buffer (pH 6·5), potassium dihydrogen phosphate in water (*ca.* 3·2 mg. phosphorus/c.c.), and fraction P2 in water (40 c.c. for each 100 c.c. of juice employed for the isolation of the enzyme). These solutions were incorporated in four digests (A—D), the compositions of which are shown in section (i) of the following table. The digests were incubated at 20° and free-phosphate estimations were made periodically; these are recorded in section (ii).

Action of fraction P2 on sodium glycerophosphate.

(i) *Compositions of digests.*

Solution.	Digest, c.c. A.	B.	C.	D.
Sodium glycerophosphate	10	10	10	10
Fraction P2	4	4	—	—
Potassium dihydrogen phosphate	1	—	1	—
Water	—	1	4	5

(ii) *Free phosphate estimations.*

Time of incubation (hours).	Free phosphorus (mg. per 15 c.c. digest). A.	B.	C.	D.
0·5	3·420	0·673	3·210	0·000
1·0	3·570	1·020	—	—
2·0	4·080	1·485	—	—
3·5	4·170	1·760	—	—
5·0	4·350	2·100	—	—
7·5	4·560	2·310	3·210	—

The inorganic phosphate liberated by enzyme action was measured (i) in the presence of potassium dihydrogen phosphate by the difference between digest (A) and (C), and (ii) in the absence of potassium dihydrogen phosphate by the difference between digest (B) and (D). These values are plotted in Fig. 1.

(b) *With sodium glycerophosphate as substrate for fraction Q3.* The above experiment was repeated using a solution of fraction Q3 in water (40 c.c. for each 100 c.c. of juice employed for the isolation of the enzyme) instead of the solution of fraction P2. No mineral phosphate was liberated by enzyme action in digest (B) in 7·5 hours, showing the absence of phosphatase activity in fraction Q3.

(c) *With dipotassium glucose-1 phosphate as substrate for fraction P2.* A digest containing the solution of fraction P2 (1·5 c.c.) used in (a), 0·1M-dipotassium glucose-1 phosphate in 0·2M-citrate buffer (pH 6·0; 1·0 c.c.), 0·5M-citrate buffer (pH 6·0; 0·5 c.c.), and starch solution (0·5 c.c., containing 0·5 mg. of starch) was incubated at 20·5° for 1 hour. There was no increase in reducing power, thus proving the absence, under these conditions, of phosphatase action on the glucose-1 phosphate.

The Influence of Fractions P2 and Q3 on the Viscosities of Starch Pastes in the Absence and in the Presence of Mineral Phosphate.—Enzyme solutions. The P2 and Q3 enzyme fractions, which had been

stored at 0° for several weeks after being freeze-dried by the standard methods given above, were each dissolved in water (20 c.c. for each 100 c.c. of juice used for the isolation of the enzymes). The P2 solution contained 14·1 units of phosphorylase/c.c., and the Q3 solution 0·8 unit of phosphorylase/c.c. In a preliminary experiment it was shown that this Q3 solution effected a maximum diminution of 83% in the A.V. (6800 A.) of amylose (B.V., 1·04) with only 2·4% "apparent conversion into maltose," a fact which established the absence of more than traces of the normal amylases from the enzyme sample (see Barker, Bourne, and Peat, Part IV, *loc. cit.*).

Starch pastes. Potato starch (dry weight, 5 g.) was dispersed in boiling water containing sodium chloride (0·5 g.). The solution was cooled and diluted to 450 c.c. with water. To half of this solution 0·2M-acetate buffer (pH 7·0; 25 c.c.) was added, giving solution (A). To the other half 0·2M-phosphate buffer (pH 6·7; 25 c.c.) was added, giving solution (B). The concentrations of starch and buffer in both (A) and (B) were 1% and 0·02M., respectively.

Viscosity measurements. The starch solution (10 c.c.; A or B) and enzyme solution (1 c.c.; P2 or Q3) were adjusted to 20°, mixed, and introduced into an Ostwald viscometer, which was immersed in a thermostat at 20°. Viscosity measurements were made at intervals and are plotted in Fig. 2. In a second series of experiments, in which the volumes of the two buffers employed were increased from 25 c.c. to 75 c.c., similar results were obtained.

The Effect of Phloridzin on the Amylose–Iodine Stain.—Amylose was stained with iodine under the standard conditions for the estimation of B.V. (Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924). The coloured solution contained amylose (1 mg./100 c.c.), iodine (2 mg./100 c.c.), and potassium iodide (20 mg./100 c.c.). A second portion of amylose was stained in the same way except that the final coloured solution contained, in addition, phloridzin (to $3·33 \times 10^{-4}$M.). The absorption values, measured immediately after the preparation of the solutions, are shown below. The amylose–iodine

The effect of phloridzin on the amylose–iodine stain.

Phloridzin concentration.	Absorption value at λ (in A.): 4300.	4700.	4900.	5200.	5500.	5800.	6000.	6800.
$3·33 \times 10^{-4}$M.	0·40	0·42	0·44	0·51	0·71	0·94	1·04	1·08
Nil	0·63	0·54	0·54	0·59	0·75	0·97	1·07	1·11

stain slowly faded in the presence of phloridzin, indicating that the initial rapid reaction of this compound with the excess of iodine (revealed in the relative absorption values) was followed by a slower reaction with the iodine involved in complex formation with the amylose.

The Effect of Phloridzin on the Conversion of Amylose by Fraction Q3.—Enzyme fraction Q3 was incubated with amylose (B.V., 1·30) under the conditions of the standard digest described by Barker, Bourne, and Peat (Part IV, *loc. cit.*). A second digest included the same components together with phloridzin ($1·5 \times 10^{-3}$M.). The course of each reaction was followed by staining, at intervals, an aliquot portion (1 c.c. ≡ 1 mg. of amylose) of the digest with iodine (6 mg.) and potassium iodide (60 mg.) in a total volume of 100 c.c. The absorption values of the stained solutions, which were measured as soon as possible after staining, are recorded in Table VII, from which it is seen that phloridzin does not inhibit the action of Q-enzyme on amylose under the conditions of the experiment.

TABLE VII.

The effect of phloridzin on the conversion of amylose (B.V., 1·30) by fraction Q3.

Concentration of phloridzin in digest.	A.V. (6800 A.) after: 15 mins.	30 mins.	63 mins.
0	0·602	0·473	0·368
$1·5 \times 10^{-3}$M.	0·602	0·467	0·352

Inhibition of P-Enzyme by Phloridzin.—(a) *Inhibition in the digest.* Fraction P2, which had been stored at 0° as the powder obtained when a solution in citrate buffer was freeze-dried by the standard technique described above, was dissolved in water (13·5 c.c. for each 100 c.c. of juice used in the preparation of the enzyme). This solution was incorporated in a digest which contained P2 solution (0·5 c.c.), 1% soluble starch solution (0·5 c.c.), 0·1M-glucose-1 phosphate in 0·2M-citrate buffer (pH 6·0; 1·0 c.c.), and water (1·5 c.c.). The digest was incubated at 35° for 12 minutes, and the reaction was then arrested by addition of 5% trichloroacetic acid solution (5·0 c.c.). After centrifuging, the free phosphate in the supernatant liquid was determined colorimetrically. The free phosphate originally present in the digest was determined by adding the trichloroacetic acid to the digest before the P2 solution was added. The mineral phosphate liberated by enzyme action was calculated by difference.

In other digests, the water (1·5 c.c.) was replaced by phloridzin solutions (1·5 c.c.) of different concentrations (0 to $2·9 \times 10^{-3}$M.), and, by comparison with the above control, the effect of phloridzin on P-enzyme activity was determined; the results are given in Table VIII. Phloridzin does not interfere with the estimation of free phosphate.

TABLE VIII.

Inhibition of P-enzyme by phloridzin present in the digest.

Concentration of phloridzin in digest (M. × 10^{-3}) ...	0·00	0·44	0·89	1·06	1·24
Inhibition (%) of P-enzyme activity	0·0	2·2	6·6	8·1	8·1

When the solution of fraction P2 was diluted ten-fold and the concentration of phloridzin in the digest was increased to $2{\cdot}67 \times 10^{-4}$M., there was 40·5% inhibition of P-enzyme activity.

(b) ***Pretreatment of fraction P2 with phloridzin.*** The experiment (a) was repeated with one variation. Fraction P2 was dissolved directly in phloridzin solutions of different concentrations (40 c.c. for each 100 c.c. of juice used in the preparation of the enzyme) and kept at room temperature for 1 hour. A portion (1·5 c.c.) of each solution was added, together with water (0·5 c.c.), to the other components of the digest and the experiment was continued as above, giving the results recorded below.

Inhibition of P-enzyme by pretreatment with phloridzin.

Concentration of phloridzin ($M. \times 10^{-4}$).		Inhibition (%) of P-enzyme activity.	Concentration of phloridzin ($M. \times 10^{-4}$).		Inhibition (%) of P-enzyme activity.
During pretreatment of the enzyme.	In the digest.		During pretreatment of the enzyme.	In the digest.	
0·00	0·00	0·0	4·14	1·78	14·0
2·07	0·89	7·4	6·20	2·67	21·3
3·10	1·33	10·3			

Precipitation of Fraction Q3 with Acetone.—The following operations were performed at 0° in a cold room. Fraction Q3, which had been freeze-dried in citrate buffer in the usual way and stored at 0° for 7 weeks, was dissolved in water (40 c.c. for each 100 c.c. of juice used in the isolation of the enzyme). Portions (2·0 c.c.) of this solution were mixed with aqueous acetone solutions (4·0 c.c.) containing different concentrations of acetone. Each precipitate was collected by the centrifuge and stirred with a mixture of 0·2M-citrate buffer (pH 7·0; 2·0 c.c.) and 0·2M-sodium hydrogen carbonate solution (1·0 c.c.), the insoluble residue being removed by the centrifuge. An aliquot portion (2·0 c.c.) of each supernatant liquid was incubated at 20·5° with amylose (14 mg.; B.V., 1·04), maltose (3 mg.), and 0·2M-citrate buffer (pH 7·0; 2·5 c.c.) in a total volume of 14 c.c. As a control a portion (2·0 c.c.) of the original Q3 solution was mixed with 0·2M-sodium hydrogen carbonate solution (1·0 c.c.) and an aliquot portion (2·0 c.c.) of the mixture was incubated with amylose under the same conditions. After 30 minutes a sample (1·0 c.c.) of each digest was stained with iodine (2 mg.)–potassium iodide (20 mg.) in a total volume of 100 c.c. The values for A.V. (6800 A.) thus obtained are tabulated below.

The precipitation of fraction Q3 with acetone at 0°.

Conc. of acetone (% by vol.)	Control	26·6	33·0	40·0
Fall (%) in A.V. (6800 A.) of amylose in 30 mins.	72·5	8·5	6·7	4·1

Autocatalysis in Polysaccharide Synthesis by P- and Q-Enzymes.—Fraction P2 was further purified by two precipitations with neutral ammonium sulphate, the fraction precipitated between ammonium sulphate concentrations of 19 and 34 g./100 c.c. being collected each time. The product was dissolved in 0·2M-citrate buffer (pH 6·0; 20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzyme) and freeze-dried. When required, the powder was dissolved in water (50 c.c. for each 100 c.c. of juice employed), giving a solution of P-enzyme which contained 2·5 units (Green and Stumpf) of phosphorylase per c.c.

Fraction Q3 was further purified by precipitating it twice with ammonium sulphate (18 g./100 c.c.) in the usual manner. The product was dissolved in 0·2M-citrate buffer (pH 6·5; 13 c.c. for each 100 c.c. of juice used for the isolation of the enzyme) and freeze-dried. When required, the powder was dissolved in water (20 c.c. for each 100 c.c. of juice employed), giving a solution of Q-enzyme which possessed 65% of the Q-enzyme activity present in the original Q3 fraction (measured by incubation with amylose and comparison with dilution curves for Q3). The solution of the purified Q-enzyme contained only 0·65 unit (Green and Stumpf) of phosphorylase per c.c.

These solutions of the purified enzymes were incorporated in digests which contained P-enzyme solution (6·75 c.c.) and/or Q-enzyme solution (6·75 c.c.), together with 0·1M-dipotassium glucose-1 phosphate (9·0 c.c.) and sufficient 0·2M-citrate buffer (pH 6·5) to make the total volume 31·5 c.c. The digests were incubated at 20° and free phosphate estimations were made at intervals, as shown in Fig. 3.

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21. *The Enzymic Synthesis and Degradation of Starch. Part VII. The Mechanism of Q-Enzyme Action.*

By S. A. Barker, E. J. Bourne, I. A. Wilkinson, and S. Peat.

The results reported in the earlier communications in this series are reviewed and correlated with the observations recorded in this paper. Evidence is given which proves, beyond reasonable doubt, that Q-enzyme functions by a non-phosphorolytic mechanism. In this and in other properties it appears to be distinct from the *iso*phosphorylase isolated (also from potatoes) by Bernfeld and Meutémédian (*loc. cit.*).

It is concluded that Q-enzyme is a transglucosidase, but not of the phosphorylase type, and that two amylopectin-synthesising systems represented by Q-enzyme and *iso*phosphorylase may exist together in the potato.

Our work on the enzymic synthesis and degradation of starch has now reached a stage where it is desirable to review the results reported in a series of earlier communications (Part I, Bourne and Peat, *J.*, 1945, 877; Part II, Bourne, Macey, and Peat, *J.*, 1945, 882; Part III, Bourne, Stitch and Peat, *J.*, 1949, 1448; Parts IV and V, Barker, Bourne, and Peat, *J.*, 1949, 1705, 1712; Part VI, Barker, Bourne, Wilkinson, and Peat, preceding paper) and to correlate them with the observations recorded in this paper.

In 1944 Haworth, Peat, and Bourne (*Nature*, **154**, 236) reported the isolation from potatoes of an enzyme (Q-enzyme) which catalysed, in association with potato phosphorylase (P-enzyme), the synthesis of amylopectin from glucose-1 phosphate. We were unaware at that time of the " branching factor " prepared from heart, liver, and yeast by Cori *et al.* (*J. Biol. Chem.*, 1943, **151**, 57) which played a similar rôle in the synthesis of glycogen. Shortly afterwards we advanced a hypothesis to account for the properties of Q-enzyme, from which it was inferred that natural amylose could be converted into amylopectin by the agency of this enzyme (Parts I and II). This hypothesis was subsequently substantiated and a preliminary account was given by Peat, Bourne, and Barker (*Nature*, 1948, **161**, 127) of the conversion of amylose into amylopectin. In no case during the isolation and purification of Q-enzyme or during the investigation of its functions was mineral phosphate introduced and for this reason we have always held the view that Q-enzyme operated by a non-phosphorolytic mechanism.

Recently, Bernfeld and Meutémédian (*Helv. Chim. Acta*, 1948, **31**, 1724, 1735) described the isolation from potatoes of an enzyme (named by them, *iso*phosphorylase) which bore some resemblance to Q-enzyme inasmuch as it played a part in the formation of amylopectin from both amylose and glucose-1 phosphate. There was nevertheless a fundamental difference between the two. Whereas we postulated that phosphate-transfer was not involved in the formation of cross linkages by Q-enzyme, the Swiss authors claimed that such transfers were an integral part of the cross-linking mechanism.

Since *iso*phosphorylase induces no qualitative change in the characteristic blue-staining property of amylose unless mineral phosphate and phosphorylase are present, Bernfeld and Meutémédian suggest that the new enzyme functions by catalysing the transfer of phosphate. They believe that P-enzyme first acts on amylose and mineral phosphate to give glucose-1 phosphate, which is then utilised by *iso*phosphorylase to establish 1 : 6-linkages, with the simultaneous liberation of mineral phosphate. The glucose-1 phosphate subsequently liberated by P-enzyme from the end of the original chain is used either (i) by *iso*phosphorylase to establish another branch, or (ii) by P-enzyme to lengthen the branch already established by *iso*phosphorylase.

The scheme for the conversion of amylose into amylopectin proposed by two of us in 1945 (Part I) was based on the observation that Q-enzyme functioned in the absence of both mineral phosphate and P-enzyme. The small impurities of mineral phosphate and P-enzyme known to be present in the samples of Q-enzyme then available were not regarded as being sufficient to play any part in the conversion. The publication of Bernfeld's views prompted us to examine Q-enzyme activity in greater detail, because, theoretically, a trace of mineral phosphate would be sufficient to facilitate the phosphorolytic mechanism proposed by him.

Conversion of Amylose into Amylopectin.—By treatment with Q-enzyme, linear amylose chains are transformed into the branched amylopectin structure. The evidence upon which this statement is based has been detailed in two earlier papers (Part V and *Nature*, 1948, **161**, 127). Briefly, Q-enzyme causes a rapid diminution of the absorption value, A.V. (6800 A.), of an amylose solution to about 13% of the original value. This red-staining solution contains only 2% of reducing sugar, expressed as maltose, and is hydrolysed at a higher initial rate by

β-amylase than is the original amylose solution, a fact in keeping with the postulate that an increase in the number of chain-ends occurs during Q-enzyme action. When the red-staining polysaccharide produced from amylose in this manner is isolated, it is indistinguishable, in its blue value, in the light-absorption curve of its iodine-stained solution, and in its limiting conversion with β-amylase, from the purest samples of natural potato amylopectin. In this conversion, (amylose ⟶ amylopectin) equilibrium lies completely, or nearly so, on the side of the branched structure.

According to Bernfeld, *iso*phosphorylase, in the presence of P-enzyme and mineral phosphate (1·35 atoms of phosphorus per $C_6H_{10}O_5$ unit), also lowers the limit conversion with β-amylase of an amylose solution (to 65%). In this reaction, the blue-staining amylose is converted into a purple-staining polysaccharide, the latter being favoured at equilibrium. Although the polysaccharide produced in this way has not yet been isolated, it probably possesses a branched structure of the amylopectin type (Bernfeld and Meutémédian, *loc. cit.*).

It was shown in Part I that as the purification of a Q-preparation proceeded, *i.e.*, as the P-enzyme content diminished, its power to effect the synthesis of polysaccharide from glucose-1 phosphate also decreased. This has been repeatedly confirmed and in the present work quantitative experiments show that the addition of glucose-1 phosphate affects neither the rate nor the end-point of conversion of amylose into amylopectin by the purest specimens of Q-enzyme (Table III). Furthermore, the degree of branching of the product of the action of Q-enzyme on amylose is the same whether the Cori ester is present or not (Table VI).

The lack of effect of mineral phosphate on the conversion of amylose into amylopectin by Q-enzyme is shown in Table II. Two parallel digests of amylose and Q-enzyme were made in acetate buffer of pH 7 at 20°. One digest contained 0·04 atom of free-phosphorus per $C_6H_{10}O_5$ unit and the other, to which mineral phosphate was added, contained 35 times as much. Nevertheless, the rate of reaction as measured by the fall of A.V. (6800 A.) was the same in the two digests. Furthermore, the free-phosphate contents did not diminish during the reaction, which was virtually complete in 150 minutes. The same lack of effect on Q-enzyme activity was shown in a second experiment in which the mineral phosphate content was increased from 0·04 to 0·18 atom of phosphorus per $C_6H_{10}O_5$ unit.

It should be pointed out that, before any specific effect of mineral phosphate on the conversion of amylose by Q-enzyme could be ascertained, it was essential to know whether salts in general influenced the reaction. Accordingly, amylose was incubated with Q-enzyme at pH 7·0 in a series of digests which differed only with respect to concentration of citrate buffer. The rate of conversion, measured by the fall in A.V. (6800 A.), rose appreciably as the buffer concentration was increased to $4·5 \times 10^{-3}$ M. and thereafter remained constant (Table I). This marked activation of Q-enzyme by salts has also been observed by Gilbert and Swallow (in the press). It was obvious that valid conclusions concerning the effect of mineral phosphate on Q-enzyme activity could be drawn only from those experiments in which other salts were present in sufficient concentration fully to activate the enzyme.

Adopting the same method as that used in studying the effects of glucose-1 phosphate and mineral phosphate, it was demonstrated that the addition of P-enzyme does not influence the conversion of amylose by Q-enzyme, if phosphate is absent and if the enzyme is activated by the presence of other ions (see Tables IV and V).

It must therefore be concluded that the presence of a relatively large amount of mineral phosphate, of P-enzyme, or of glucose-1 phosphate does not influence the conversion of amylose into amylopectin by Q-enzyme, with respect either to rate or to type of reaction. If now Q-enzyme operates as an *iso*phosphorylase the addition of any of these three agents would be expected markedly to affect the rate of conversion as measured by the change in A.V. (6800 A.). The fact that this does not happen furnishes ample support for our view that Q-enzyme does not operate by a mechanism of phosphate transfer in the synthesis of cross-linkages.

Hehre (*J. Biol. Chem.*, 1949, **177**, 267) has reported that an enzyme present in extracts of *Neisseria* converts crystalline corn amylose into a glycogen-like polysaccharide without the release of reducing sugars and without the addition of mineral phosphate. This enzyme would appear to have the character more of Q-enzyme than of *iso*phosphorylase.

Attention was next directed to the question of reversal of synthesis, *i.e.*, to the scission of cross-linkages and the part, if any, played by phosphate in the process. For this purpose the action of Q-enzyme on amylopectin and on the limit dextin-A was studied.

It was important in these experiments to be able to assess the degree of branching in the products of Q-enzyme activity. Such comparisons of extent of ramification were made by measuring the limit of β-amylolysis of each specimen. The smaller the proportion of branches

in the substrate, the higher will be the β-amylase conversion limit. It must be borne in mind, however, that no β-amylase preparation at present available is entirely free from α-amylase and for this reason β-amylolysis must be carried out at an acid pH (usually, 4·7) at which the α-amylase is inoperative (see Peat, Whelan, and Pirt, *Nature*, **1949**, **164**, 499).

When thymol-amylopectin (blue value, B.V., 0·215) was incubated for 3 hours at pH 7·0 with fraction Q3 there was less than 1% increase in the content of reducing sugar, expressed as maltose. The polysaccharide product gave rise, by β-amylolysis at pH 4·7, to a limit dextrin and 47% of maltose, compared with 53% of maltose in the case of the parent thymol-amylopectin (Table VII). Little or no scission of the cross-links could have occurred. Indeed Q-enzyme treatment had brought about a slight increase in the degree of branching, presumably by the conversion into amylopectin of the small amylose impurity known to be present in thymol-amylopectin (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687). Identical results were obtained from a similar experiment in which mineral phosphate (1·35 atoms of phosphorus per $C_6H_{10}O_5$ unit) was introduced during the treatment of amylopectin with Q-enzyme (Table VII). It is clear that, if the synthesis of cross-links by Q-enzyme is a reversible process, then at equilibrium there is an overwhelming preponderance of the branched structure and that this equilibrium is not influenced by the presence of phosphate.

The ability of highly purified Q-enzyme (fraction Q5) to hydrolyse the cross-links of dextrin-A has been investigated (Table VIII). Although there was only a slight development of reducing power, corresponding to 1% conversion into maltose, when dextrin-A was treated for 3 hours with enzyme fraction Q5, the dextrin did become somewhat more susceptible to β-amylolysis. Whereas the original dextrin gave 2% of maltose with β-amylase, the product of Q-enzyme action gave 11·5% of maltose. It was shown once again that the presence of mineral phosphate (1·35 atoms of phosphorus per $C_6H_{10}O_5$ unit) did not materially alter the result. In this respect the action appears to be different from that of *iso*phosphorylase on the dextrin. While it is clear that slight hydrolysis, as opposed to phosphorolysis, of the dextrin had occurred during the Q-enzyme treatment, it is by no means certain that there had been a specific scission of the cross-links by Q-enzyme, for it is well-known that a very minute amount of α-amylase impurity in the enzyme sample could, by scission of 1 : 4-linkages in the "inner" polysaccharide chains, have caused the observed increase in the degree of β-amylolysis of the dextrin (Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924). We therefore note that the action of Q-enzyme on dextrin-A is not facilitated by the presence of mineral phosphate, but, until further information is available, we hestitate to attribute the action on dextrin-A to the scission of 1 : 6-linkages by Q-enzyme.

As is to be expected, whole starch behaves, in most respects, like a mixture of amylose and amylopectin under the action of Q-enzyme which simply transforms the amylose component of potato starch into amylopectin and leaves the amylopectin component essentially unchanged, so that the whole of the starch is converted into the ramified structure (Parts II and V). Q-Enzyme rapidly diminishes the viscosity of a starch paste (Parts I and VI), whereas *iso*phosphorylase does not (*Helv. Chim. Acta*, **1948**, **31**, 1724). It appears improbable that the liquefying property of Q-enzyme can be attributed to either α- or β-amylase, because (*a*) reducing sugars do not appear, (*b*) the solution never becomes achroic, and (*c*) the polysaccharide product is indistinguishable from natural amylopectin. The effect of Q-enzyme in lowering starch viscosity is not influenced by the addition of mineral phosphate (Part VI, Fig. 2).

Purity of the Q-Enzyme Preparations.—It was fully appreciated, early in this work, that the conclusions concerning the mechanism of starch synthesis and degradation depend largely on the degree of enzymic purity. In particular it was important that Q-enzyme preparations should be as free as possible from amylases. The most persistent impurity is α-amylase and tests for its presence are complicated by the doubt, which still exists, whether Q-enzyme *per se* liberates reducing groups during the conversion of amylose into amylopectin or whether this small "apparent conversion into maltose" (*ca.* 2%) is caused by a trace of α-amylase. It is certain, however, that if α-amylase is still present in the purest Q-enzyme samples, it is there in such minute quantities as not to affect the validity of the conclusions we have drawn.

In Parts IV and V of this series and also in the present paper, evidence has been presented to show that Q-enzyme, even at the Q1 stage, contains no more than a trace of either α- or β-amylase, since it effects an 87% reduction in A.V. (6800 A.) of amylose with the concomitant liberation of only 2% of reducing sugar (expressed as maltose). At this point, the solution is stained red by iodine, and does not subsequently become achroic. Fraction Q1 is free from maltase (Part IV), while fraction Q3 contains no phosphatase (no action on sodium glycerophosphate, Part VI). Fraction Q3 is normally contaminated with a little P-enzyme (Part VI),

but, if during the course of its isolation it is freeze-dried at the Q1 stage in the absence of a buffer, the P-enzyme impurity is preferentially destroyed and in this way samples of fraction Q3 were obtained which were devoid of P-enzyme activity when tested by the method of Green and Stumpf (*J. Biol. Chem.*, 1942, **142**, 355).

Synthesis of Amylopectin from Glucose-1 Phosphate.—Bourne and Peat (1945) advanced the theory that P-enzyme first builds up linear polysaccharide chains by the end-wise apposition, in α-1 : 4-linkage, of glucose units derived from glucose-1 phosphate, and that these amylose-type molecules then serve as a substrate for Q-enzyme, which converts them into amylopectin in the same way as it transforms natural amylose into amylopectin. There could be no doubt that the product of the joint action of P- and of Q-enzyme on glucose-1 phosphate was amylopectin, for this synthetic polysaccharide was isolated and could not be distinguished, in its blue value, in its limit conversion with β-amylase, and in its average chain-length, as determined by end-group assay, from natural amylopectin (Part I).

Bernfeld and Meutémédian also regard the first stage in amylopectin synthesis as the formation, by P-enzyme, of linear chains. The second stage is pictured as the establishment of branch points by the addition to these chains, by *iso*phosphorylase, of single glucose units (derived from glucose-1 phosphate) in 1 : 6-linkage. It is suggested that the branches thus introduced are lengthened by subsequent P-enzyme action and in this way give rise to the " outer " chains of amylopectin. There is some doubt, however, whether the final stage in this scheme of synthesis would in fact occur, for it is known that at least three, and proably more, 1 : 4-linked glucose units must be present in an " outer " chain before the structure will serve as a template for P-enzyme (Weibull and Tiselius, *Arkiv Kemi, Min., Geol.*, 1945, **19**, *A*, No. 19). This question of the relation between structure and activating power has been discussed more fully in Part III of this series.

We have always maintained that Q-enzyme *per se* cannot utilise glucose-1 phosphate as a substrate, because increased purification of the enzyme invariably results in a decreased ability to liberate mineral phosphate from the Cori ester. Indeed this has been the method by which we have measured the progressively decreasing impurity of P-enzyme in Q-enzyme samples. Samples of Q-enzyme have now been prepared in which P-enzyme cannot be detected by the method of Green and Stumpf (*loc. cit.*), which involves incubating the enzyme sample with glucose-1 phosphate in the presence of starch and measuring the amount of mineral phosphate liberated. It follows that Q-enzyme cannot utilise glucose-1 phosphate even in the presence of the template chains furnished by starch. On the other hand, Bernfeld and Meutémédian (*loc. cit.*) demonstrated that *iso*phosphorylase does liberate mineral phosphate from the Cori ester. In this respect Q-enzyme again appears to differ from *iso*phosphorylase, but its behaviour is similar to that of Cori's branching factor from liver (*J. Biol. Chem.*, 1943, **151**, 57).

Conclusions.—The evidence presented furnishes proof that Q-enzyme does not operate by a mechanism involving phosphate, and cannot, therefore, be an *iso*phosphorylase. The conclusion appears to be inevitable that two types of enzyme are responsible for the synthesis of cross-links in branched polysaccharides, one type (*iso*phosphorylase) functioning by means of phosphate transfers and the other (Q-enzyme, Cori's " branching factor ") by a trans-glucosidase action which is independent of phosphate. It is not altogether surprising that there should be two modes of synthesis for it is well-known that starch is degraded by amylolytic as well as by phosphorolytic enzymes.

Q-Enzyme would thus be regarded as belonging, in common with other enzymes concerned in polysaccharide synthesis, to the class of trans-glycosidases, of which the phosphorylases constitute only one type (see Doudoroff, Barker, and Hassid, *J. Biol. Chem.*, 1947, **168**, 725). As discussed by us in Part V of this series, the scission of a 1 : 4-link in the amylose chain probably occurs simultaneously with the formation of a 1 : 6-link and thus appreciable quantities of short unbranched chains (" pseudo-amylose ") are not detected.

Experimental.

Analytical Methods.—The analytical methods employed in this work were discussed in Part IV.

Fractionation of Starch.—The amylose and amylopectin samples were isolated from potato starch by fractional precipitation of the former with thymol (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687).

Isolation of P- and Q-Enzymes from Potatoes.—Details of the method employed for the isolation of these enzymes were given in the preceding paper.

Ionic Activation of the Action of Q-Enzyme on Amylose.—Enzyme fraction Q3 was freeze-dried in the presence of citrate buffer (pH 7·0) according to the standard method described in the preceding paper. When required, the dry powder was dissolved in water (80 c.c. for each 100 c.c. of juice used in the isolation of the enzyme). This Q3 solution, which was $3{\cdot}13 \times 10^{-3}$M. with respect to citrate buffer,

was incorporated in digests containing amylose (14 mg.; B.V. 1·04), maltose (3 mg.), Q3 solution (2·0 c.c.), 0·2M-citrate buffer (pH 7·0; varying volumes), and water to make the total volume 14 c.c. in each case. The digests were incubated at 20·5° and, at intervals, aliquot portions (1 c.c. ≡ 1 mg. of amylose) were stained with iodine (2 mg.)–potassium iodide (20 mg.) in a total volume of 100 c.c. The values of A.V. (6800 A.) thus obtained were related to the concentrations of buffer employed, as is shown in Table I. In addition to these different concentrations of citrate buffer, there were other salts present in constant strength in each digest, namely sodium sulphate ($1{\cdot}12 \times 10^{-2}$M.) (arising from dissolution of the amylose in aqueous sodium hydroxide and neutralisation of the solution with sulphuric acid) and ammonium sulphate (a small residue left from precipitation of the enzyme). The Q3 fraction used in these digests had been shown, in a separate experiment, to effect a fall of 88% in the A.V. (6800 A.) of the amylose with an "apparent conversion into maltose" of only 3·0% and thus to be essentially free from the normal amylases.

TABLE I.

Ionic activation of the action of Q-enzyme on amylose.

Molarity of citrate buffer (pH 7·0) in digest ($\times 10^2$).	Fall (%) in A.V. (6800 A.) of amylose. 20 mins.	45 mins.	Molarity of citrate buffer (pH 7·0) in digest ($\times 10^2$).	Fall (%) in A.V. (6800 A.) of amylose. 20 mins.	45 mins.
0·45	40·4	61·9	3·33	51·8	69·5
1·16	47·0	65·6	4·76	53·3	69·8
1·88	48·8	66·2	6·18	54·2	69·8

When the results (Table I) were plotted it was evident that the minimum concentration of citrate buffer necessary for full activation of the enzyme was $4{\cdot}5 \times 10^{-2}$M.

Effect of Mineral Phosphate on the Rate of Conversion of Amylose by Q-Enzyme.—Fraction Q1 was dissolved in a little water and freeze-dried, a process which diminished considerably the small amount of P-enzyme impurity (see Part IV). When required, the dry powder was dissolved in water (17 c.c. for each 100 c.c. of juice used in the isolation of the enzyme). An aliquot portion (5 c.c.) of this enzyme solution was incubated at 20·5° with amylose (20 mg.; B.V. 1·30; dissolved in sodium hydroxide and neutralised with sulphuric acid, as described in Part IV), maltose (8 mg.), and M-acetate buffer (pH 7·0; 5 c.c.) in a digest having a total volume of 50 c.c. At intervals, portions (2·5 c.c. ≡ 1 mg. of amylose) were stained with iodine (2 mg.)–potassium iodide (20 mg.) in a final volume of 100 c.c. The values for % fall of A.V. (6800 A.) are shown, together with the increase in copper reducing value (expressed as maltose), in Table II. The free-phosphorus content of the digest remained constant at 0·170 mg., corresponding to 0·044 atom of phosphorus per $C_6H_{10}O_5$ unit in the amylose. This impurity of mineral phosphate had been introduced mainly with the enzyme solution.

A second digest (total volume, 50 c.c.), which was incubated simultaneously with that already described, contained, in addition to the above components, $3{\cdot}462 \times 10^{-2}$M-phosphate buffer (pH 7·0; 5 c.c.). This digest contained 0·18 atom of free phosphorus per $C_6H_{10}O_5$ unit. The values of A.V. (6800 A.) and "apparent conversion into maltose" were very similar to those recorded in the first digest (Table II).

In a second experiment with a fresh enzyme solution 1·35 atoms of free phosphorus per $C_6H_{10}O_5$ unit were added. The rate of conversion of the amylose was not increased even by this high concentration of mineral phosphate (Table II).

TABLE II.

Effect of mineral phosphate on the conversion of amylose by Q-enzyme.

Experiment.	Molarity of acetate buffer in digest.	Atoms of free phosphorus per $C_6H_{10}O_5$ unit in the amylose.	Fall (%) in A.V. (6800 A.) of amylose. 25 mins.	150 mins.	Apparent conversion into maltose (%) in 150 mins.
First	0·1	0·04	73·7	84·2	1·0
"	0·1	0·18	74·0	84·3	1·2
Second	0·1	0·04	72·9	86·0	0·0
"	0·1	1·39	73·0	86·4	0·0

Effect of Glucose-1 Phosphate on the Rate of Conversion of Amylose by Q-Enzyme.—Fraction Q3 was prepared from a sample of fraction Q1 which had been freeze-dried as described above. It was dissolved in water (20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzyme) and gave a solution in which phosphorylase could not be detected by the method of Green and Stumpf (*J. Biol. Chem.*, 1942, **142**, 355). This Q3 solution (4·5 c.c.) was incorporated in two digests (volume 50 c.c.) similar to those used in the previous experiment. The control digest was found to contain 0·032 mg. of free phosphorus, *i.e.*, 0·0083 atom of phosphorus per $C_6H_{10}O_5$ unit. The second digest contained the same components as the control, together with 0·1M-dipotassium glucose-1 phosphate solution (1·0 c.c.), *i.e.*, 0·81 mole of the Cori ester per $C_6H_{10}O_5$ unit. The digests were incubated at 20·5° and aliquot portions were stained with iodine in the manner described above. Glucose-1 phosphate did not influence the rate of fall of A.V. (6800 A.), as is shown in Table III.

Effect of Phosphorylase on the Rate of Conversion of Amylose by Q-Enzyme.—The enzyme fractions P2 and Q3 had been freeze-dried in citrate buffer by the standard methods described in the preceding paper. They were dissolved as required in water (20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzymes), giving solutions which contained, respectively, 14·05 and 0·78 units (Green

and Stumpf) of phosphorylase per c.c. These enzyme solutions were incorporated in two digests, prepared in the usual way and having the compositions shown in Table IV. The digests were incubated at 20·5° and, at intervals, aliquot portions (1 c.c. ≡ 1 mg. of amylose) were stained with iodine as usual. As will be seen from Table V, the presence of P-enzyme did not influence the rate of fall of A.V. (6800 A.).

TABLE III.

Effect of glucose-1 phosphate on the rate of conversion of amylose (B.V. 1·30) by Q-enzyme.

Molarity of acetate buffer in digest.	Moles of Cori ester per $C_6H_{10}O_5$ unit.	Fall (%) in A.V. (6800 A.) of amylose. 90 mins.	105 mins.	180 mins.
0·1	Nil	71·7	73·1	78·1
0·1	0·81	71·5	72·8	77·1

TABLE IV.

Effect of P-enzyme on the rate of conversion of amylose by Q-enzyme. Composition of the digests.

	Volumes of component solutions, c.c.					
Digest.	Fraction P2.	Fraction Q3.	Amylose (B.V. 0·98) (14 mg./6·5 c.c.).	0·2M-Citrate buffer (pH 7·0).	Maltose (3 mg./1·5 c.c.).	Water.
A	Nil	1·0	6·5	1·5	1·5	3·5
B	1·0	1·0	6·5	0·5	1·5	3·5

TABLE V.

Effect of P-enzyme on the rate of conversion of amylose by Q-enzyme.

Digest.	Molarity of citrate in digest.	Units of P-enzyme (Green & Stumpf) in digest.	Fall (%) in A.V. (6800 A.) of amylose. 30 mins.	67 mins.	144 mins.	Apparent conversion into maltose (%).
A	$3·04 \times 10^{-3}$	0·78	68·4	76·3	83·1	2·4
B	$3·04 \times 10^{-3}$	14·83	66·3	75·7	82·9	1·8

Effect of Glucose-1 Phosphate on the Degree of Branching of the Polysaccharide Produced from Amylose by Q-Enzyme.—Fraction Q3 was prepared from a sample of fraction Q1 which had been dissolved in water and freeze-dried. The Q3 sample was dissolved in water (20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzyme) and gave a solution in which phosphorylase could not be detected by the method of Green and Stumpf (*loc. cit.*). This enzyme solution (4·5 c.c.) was introduced into two of three digests, which were prepared in the usual way; all three contained amylose (20 mg.; B.V. 1·30), maltose (8 mg.), and M-acetate buffer (pH 7·0; 5 c.c., being sufficient to ensure complete ionic activation of the Q3) in a total volume of 24 c.c. A second series of three digests (24 c.c.) was prepared, each containing, in addition to the components already listed, 0·1M-dipotassium glucose-1 phosphate (1·0 c.c.), *i.e.*, 0·81 mole of the Cori ester per $C_6H_{10}O_5$ unit in the amylose. These six digests were incubated at 20·5° for different times, and N-acetic acid (5 c.c.) was then added to each; this lowered the pH to 4·7 and thus almost completely inactivated the Q-enzyme. To each digest a 0·2% solution

TABLE VI.

Effect of glucose-1 phosphate on the degree of branching of the polysaccharide produced by the action of Q-enzyme on amylose.

Fraction Q3 (free from P-enzyme) + amylose (B.V. 1·30) at pH 7·0. Time of incubation before the addition of β-amylase (hours).	Mole of Cori ester per $C_6H_{10}O_5$ unit.	Apparent conversion into maltose (%) at end of incubation.	β-Amylolysis of product at pH 4·7. Limit conversion into maltose (%).
0	Nil	—	89
0	0·81	—	89
1·5	Nil	—	44
1·5	0·81	—	47
3·0	Nil	1·3	40
3·0	0·81	0·0	45

(10 c.c.) of soya-bean β-amylase was then added, the volume adjusted to 50 c.c., and incubation continued until no further increase in reducing power occurred. The liberation of maltose was followed by means of the Shaffer-Hartmann reagent, and to the figures thus obtained small corrections were applied for the reducing powers of the original components of the digests. Table VI shows that the presence of glucose-1 phosphate does not influence, within the experimental error, the structure of the polysaccharide produced by Q-enzyme acting on amylose.

Action of Q-Enzyme on the Cross-linkages of Amylopectin.—The Q3 fraction employed was the same as that used in the last experiment. Portions (4·5 c.c.) of an aqueous solution (20 c.c. for each 100 c.c. of juice used in the isolation of the enzyme) of the enzyme were introduced into three of four identical digests, which were prepared in the usual manner; all four contained amylopectin (20 mg.; B.V. 0·215), maltose (8 mg.) and M-acetate buffer (pH 7·0; 5 c.c., being sufficient fully to activate the enzyme) in a total volume of 30 c.c. A series of four similar digests (30 c.c.) was prepared, each containing, in addition to the above components, $3·33 \times 10^{-4}$M-phosphate buffer (pH 7·1; 5 c.c.), *i.e.*, 1·35 atoms of free phosphorus per $C_6H_{10}O_5$ unit in the amylopectin. The eight digests were incubated at 20·5° for different periods, adjusted to pH 4·7 with acetic acid, mixed with a 0·2% solution (10 c.c.) of soya-bean β-amylase diluted to 50 c.c., and further incubated until maximum conversion into maltose had occurred. The maltose liberated was estimated by the Shaffer–Hartmann method, allowance being made for the reducing powers of the digest components.

TABLE VII.

Action of Q-enzyme on the cross-links of amylopectin.

Fraction Q3 (free from P-enzyme) + amylopectin (B.V. 0·215) at pH 7·0.			β-Amylolysis of product at pH 4·7.
Time of incubation before the addition of β-amylase (hours).	Moles of free phosphorus per $C_6H_{10}O_5$ unit in the amylopectin.	Apparent conversion into maltose (%) at end of incubation.	Limit conversion into maltose (%).
0	Nil	—	53
0	1·35	—	53
0·5	Nil	0·0	54
0·5	1·35	0·0	47
1·5	Nil	0·0	48
1·5	1·35	0·0	47
3·0	Nil	1·3	47
3·0	1·35	0·0	47

Table VII shows (i) that the Q-enzyme slightly increased the degree of branching of the "thymol"-amylopectin by an amount consistent with the conversion of the small amylose impurity in the polysaccharide into amylopectin and (ii) that the presence of mineral phosphate did not influence the conversion.

Action of Q-Enzyme on the Cross-linkages of Dextrin-A.—Fraction Q5 (see preceding paper), isolated from 100 c.c. of potato juice, was dissolved in 0·2M-citrate buffer (pH 6·5; 13 c.c.) and freeze-dried. When required, the powder was redissolved in water (100 c.c.), giving a solution which contained only 0·014 unit [Green and Stumpf] of phosphorylase per c.c.

The previous experiment was repeated using this enzyme solution with dextrin-A, prepared by β-amylolysis of thymol-amylopectin, as substrate. The results are shown in Table VIII.

TABLE VIII.

Action of Q-enzyme on the cross-links of dextrin-A.

Fraction Q5 + dextrin-A at pH 7·0.			Increase in conversion into maltose (%) during β-amylolysis at pH 4·7 for 3½ hours.
Time of incubation before the addition of β-amylase (hours).	Moles of free phosphorus per $C_6H_{10}O_5$ unit in dextrin-A.	Apparent conversion into maltose (%) at end of incubation.	
0	0	0·0	2·0
0	1·35	0·0	3·5
0·5	0	0·0	6·5
0·5	1·35	0·0	5·5
1·5	0	0·0	10·5
1·5	1·35	0·0	9·5
3·0	0	1·0	11·5
3·0	1·35	2·0	9·5

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22. *A Study of the Action of Bromine on the Silver Salts of Organic Acids.*

By J. W. H. Oldham.

The action of bromine, dissolved in dry carbon tetrachloride, on the silver salts of five classes of organic acid has been investigated. (1) Monobasic aliphatic acids are decarboxylated with production of monobromides. This reaction gives a promising method of preparing *sec*-pentyl halides, and is being further investigated. (2) Monobasic aromatic acids give less monobromide, and considerable quantities of the ester (formed by the loss of two atoms of silver and one molecule of carbon dioxide, from two molecules of the silver salt). (3) Monobasic aliphatic keto-acids, having the keto-group in or beyond the β-position, give about 50% of the monobromide, together with free parent acid and its bromination products. (4) Dibasic aliphatic acids give dibromides and/or lactones and bromo-acids, according to their structure. This reaction provides a method, better than any hitherto described, of obtaining alkylene dibromides where the bromine atoms are five or more carbon atoms apart. (5) Dibasic aromatic acids are sometimes unaffected by the reagent; others give some of the expected dibromide and larger quantities of the free parent acid.

For groups (1) and (2), and for some acids of group (4), the main reaction products from one or more members have been fully identified, either as known crystalline substances or, where they are oils, by conversion into known crystalline derivatives. The essentially similar analyses and properties of the products from other members of these groups point to the reactions being parallel. In group (3) and in the remaining acids of group (4) this procedure has been omitted owing to the unsatisfactory nature of the reaction. In group (5) little reaction occurred and crystalline products were recovered.

α-iso*Amyladipic* (*7-methyloctane-1 : 4-dicarboxylic*), m. p. 67—68°, and α-iso*amylglutaric* (*6-methylheptane-1 : 3-dicarboxylic*) *acid*, an oil, are described.

An earlier paper (Oldham and Ubbelohde, *J.*, 1941, 368) describes a new series of acyl derivatives of iodine prepared by the action of this halogen on the silver salts of aliphatic monobasic acids in the entire absence of water.

Although the action of bromine on the silver salts of the higher fatty acids has been studied by Mehta, Mehta, and Thosar (*J. Indian Chem. Soc.*, Indian Edn., 1940, 137) and that on the half esters of many dibasic aliphatic acids by Hunsdiecker and Hunsdiecker (*Ber.*, 1942, **75**, *B*, 291), very little has been published on the behaviour of the silver salts of aromatic or dibasic aliphatic acids. The work of the German authors on silver sebacate and adipate is in good agreement with the work described below. The behaviour of the following groups of compounds is now described: (1) monobasic aliphatic acids, (2) monobasic aromatic acids, (3) monobasic aliphatic monoketo-acids, (4) dibasic aliphatic acids, and (5) dibasic aromatic acids.

The advantages of the bromine reaction over the iodine reaction lie in the greater solubility of bromine, the greater speed of reaction, the production of fewer by-products, and the greater stability and lower boiling points of the bromo-compounds. The disadvantages are that with unsaturated acids it forms additive compounds, and with aliphatic keto-acids it has now been shown to form bromo-substituted derivatives with the consequent evolution of hydrogen bromide which, in turn, decomposes the silver salt to the original acid, causing a diminution of the yield. The choice of solvent for bromine is limited practically to carbon disulphide and carbon tetrachloride. In apparent disagreement with Hunsdiecker and Hunsdiecker (*loc. cit.*), bad yields were obtained in carbon disulphide, large quantities of the acid being recovered unchanged. Carbon tetrachloride was used throughout the present work, although the closeness of its boiling point to that of the lower alkyl bromides made the isolation of these products laborious.

It has already been shown (Oldham and Ubbelohde, *loc. cit.*) that the reaction of iodine with the silver salts of the monobasic aliphatic acids proceeds according to the equation

$$3R{\cdot}CO_2Ag + 2I_2 \longrightarrow (R{\cdot}CO_2)_2I + 3AgI \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and that the unstable iodine acyls decompose rapidly in two ways simultaneously, the proportion of iodine present determining whether the ester, $R{\cdot}CO_2R$ (hereafter referred to as the Simonini ester), or the alkyl iodide, RI, predominate in the product:

$$(R{\cdot}CO_2)_2I \longrightarrow R{\cdot}CO_2R + RI + 2CO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$(R{\cdot}CO_2)_2I + I_2 \longrightarrow 3RI + 3CO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

It will be seen from equation (1) that three equivalents of iodine suffice to convert all the silver present into silver iodide; if an excess of iodine is present, further reaction occurs according to equation (3).

With bromine, on the other hand, it has now been shown that the reaction cannot be stopped at stage (1), no doubt because of the very great instability of the bromine acyls which, unlike the iodine acyls usually decompose rapidly at room temperature. For compounds of shorter chain length see Birkenbach, Goubeau, and Berninger (*Ber.*, **1932**, **65**, **1339**) and Bockemuller and Hoffman (*Annalen*, **1935**, **519**, 165) who indicate that the decomposition is even more rapid. Special experiments were carried out with silver hexoate and sebacate from which, the proportion of bromine being less than two equivalents to one of silver salt, the formation of Simonini ester would be expected according to equation (4), which summarises the equivalents of equations (1) and (2):

$$3R{\cdot}CO_2Ag + 2Br_2 \longrightarrow R{\cdot}CO_2R + RBr + 3AgBr + 2CO_2 \quad . \quad . \quad . \quad . \quad (4)$$

Contrary to expectation, the reaction actually took place according to equation (5), which summarises the equivalents of equations (1) and (3):

$$R{\cdot}CO_2Ag + Br_2 \longrightarrow RBr + AgBr + CO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

An equivalent amount of the silver salt was recovered unchanged. As both these salts gave similar results, only the experiments with silver hexoate are described.

In spite of the precautions taken to exclude water, some of the free parent acid, as distinct from unchanged silver salt, usually appears in the products. This can be accounted for by equation (6):

$$6R{\cdot}CO_2Ag + 3H_2O + 3Br_2 \longrightarrow 6R{\cdot}CO_2H + 5AgBr + AgBrO_3 \quad . \quad . \quad . \quad (6)$$

When the reactions were carried out under conditions of less rigorous drying, as much as 50—60% of unchanged acid was found in the product; it can readily be seen that in small-scale experiments the air in the vessel will contain as much water as in a larger-scale experiment carried out in the same vessel, and that this water will have a relatively greater effect on the reaction.

In the detailed discussion which follows, the yields given represent the average from several experiments, the results of which, while in close agreement, were never identical. The figures are percentages of the calculated theoretical yield, any unchanged silver salt having been allowed for.

Group (1). *Monobasic Aliphatic Acids.*—With silver diisoamylacetate (2 : 8-dimethylnonane-5-carboxylate) and *cyclo*hexanecarboxylate the actual yield of bromide was low; this may have been due to its volatility, as in these cases it was actually isolated; with the hexoate and ββ-dimethylbutyrate however, the bromide was removed, along with the solvent, on drying *in vacuo* at 100°, its yield being calculated by difference.

Group (1) *acids.*

Silver salt.	Loss of CO_2, %.	Unchanged acid, %.	Bromide, %.	Simonini ester, %.
Hexoate	91·4	5·5	92	2·4
ββ-Dimethylbutyrate	86·5	13·2	82·9	3·9
Diisoamylacetate	85·9	13·2	66·6	4·1
Stearate and palmitate •	93·6	5·5	89·4	0
*cyclo*Hexanecarboxylate	84·2	13·2	57·5	6·4

Equation (5) accounts for almost all the reaction of monobasic aliphatic acids (see table); when a ring is introduced, as in the *cyclo*hexanecarboxylate, more of the Simonini ester is formed, showing that reaction (4) is beginning to compete.

This reaction provides a convenient method of preparing the hitherto rather inaccessible halides of *neo*pentane, since ββ-dimethylbutyric acid is fairly easily prepared by the oxidation (best, by ozone) of diisobutene. In view of the importance of these compounds this is being further investigated.

Group (2). *Monobasic Aromatic Acids.*—Bromobenzene is volatile *in vacuo* at 100°, but it was isolated contaminated with less than 10% of carbon tetrachloride. The low yield of benzyl bromide may be due to its volatility *in vacuo* at 100°. The results show that here reaction (4) is competing strongly with reaction (5).

• In cases marked thus, the principal products have been completely identified, being themselves crystallised or converted into crystalline derivatives. In other cases identity was partly inferred by analogy.

Silver salt.	Loss of CO_2, %.	Recovered acid, %.	Bromide, %.	Simonini ester, %.
Benzoate	66·1	10·6	45·8	43·9
Phenylacetate	74·5	14·0	53·7	21·0
o-Nitrobenzoate *	79·1	10·7	71·2	20·4

Group (3). *Monobasic Aliphatic Monoketo-acids.*—In this group, the reaction with bromine takes an unusual course, the greater part of the product consisting of the free parent acid, in spite of the fact that the conditions of rigorous drying were the same as in the other groups; in this reaction bromine substitution also occurs, leading to the formation of a bromo-acid. Similar results were obtained with 3-ketononane-1-carboxylic acid. With iodine on the other hand, the Simonini ester seemed to predominate in the product.

Silver salt.	Loss of CO_2, %.	Free parent acid, %.	Bromo-acid, %.	Bromide, %.	Simonini ester, %.
9-Ketodecane-1-carboxylate	42·0	50·7	4·8	39·8	Probably none

Group (4). *Dibasic Aliphatic Acids.*—If only one carboxyl group of dibasic acids is replaced by bromine, a bromo-acid results. With symmetrical acids, such as adipic, only one product, δ-bromovaleric acid can be formed; with asymmetrical acids on the other hand, such as α-methylglutaric acid, there are two possibilities: γ-bromovaleric and 4-bromobutane-2-carboxylic acid. The same considerations apply where one carboxyl group reacts with the halogen to give a lactone. Adipic acid could give only δ-valerolactone, while α-methylglutaric acid could give γ-valerolactone or α-methyl-γ-butyrolactone.

The salts in the annexed table are arranged in sub-divisions according to the distance between the carboxyl groups.

Group (4) *Acids.*

Silver salt, Sub-group A.	Loss of CO_2, %.	Dibromide, %.	Bromo-acid, %.	Lactone, %.	Free parent acid, %.
Sebacate *	94·5	81·3	7·3	0	0
Azelaate	93·7	82·5	6·7	0	3·0
Pimelate	78·3	44·1	20·2	—	1·9
Sub-group B.					
α-*iso*Amyladipate	64·2	33·1	28·6	30·5	1·7
Adipate *	80·1	28·7	4·4	46·1	—
Sub-group C.					
α-*iso*Amylglutarate	58·7	15·8	18·6	60·5	2·8
ββ-Dimethylglutarate *	64·8	9·8	—	50·6	—
α-Methylglutarate	50·0	6·6	5·1	87·0	—
Glutarate	47·2	3·0	—	69·4	1·6
Sub-group D.					
*iso*Amylsuccinate	68·2	25·0	—	—	—
Methylsuccinate	77·0	12·6	—	—	—
Succinate	65·2	—	19·6	—	21·4
Sub-group E.					
Benzylmalonate	10—15	—	—	—	—

Sub-group A. Where the carboxyl groups are five or more carbon atoms apart the reaction is more like that of the aliphatic monobasic salts, the dibromide predominating in the product, some bromo-acid being also formed. In the case of pimelic acid some products of an ester-like type are produced which are still being investigated (see Experimental section).

Sub-group B. Here the yield of dibromide is diminished; the formation of a considerable quantity of lactone shows that, though both carboxyl groups apparently can react, the process tends to stop after one has reacted; this is even more marked in the next sub-group. In these cases, equation (4) becomes modified, and the lactone instead of the Simonini ester is formed.

$$AgO_2C\cdot[CH_2]_{3\text{-}4}\cdot CH_2\cdot CO_2Ag + Br_2 \longrightarrow OC\overset{\frown O\frown}{\cdot[CH_2]_{3\text{-}4}\cdot CH_2} + 2AgBr + CO_2 \quad . \quad . \quad (7)$$

Silver adipate could not be dealt with by ordinary methods as, although the neutral fraction could be obtained by extracting the reaction product with aqueous sodium hydroxide, all attempts to recover the acid resulted in extremely bad yields. The alkaline

* See footnote, p. 101.

extraction method was therefore only used to determine the amount of bromo-acid present. The procedure finally adopted consisted in heating the whole of the carbon tetrachloride extract with hydrogen bromide in a sealed tube at 100°, whereupon all the lactone present was converted into the bromo-acid. The mixture could then be separated into acid and neutral fractions with a total recovery of over 95%. Both fractions were converted in good yield into their crystalline phenoxy-derivatives.

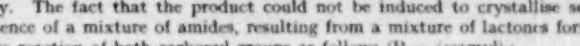
Further, silver adipate seems particularly hard to dry. On a 10-g. scale, 20—35% of the amount of adipic acid theoretically present in the original silver adipate taken was recovered from an acetone extract of the silver residues; at the same time these residues showed no appreciable oxidising power, which would be expected from equation (6). For this reason, the amount of recovered adipic acid (calculated as silver salt) has been deducted from the original weight of silver adipate when assessing the figures quoted in the table.

Sub-group C. Here the lactone is the chief product, showing that reaction (7) predominates.

Sub-group D. Here no unimolecular lactone can be formed. There is however, some evidence for the formation of di- or poly-molecular compounds of the Simonini-ester type. More dibromide is formed than in the previous group. Nearly 50% of the product was a complex mixture of acids, the nature of which has not so far been elucidated.

Sub-group E. Here the reaction appears to follow an entirely different course. Although only 10—15% of the carbon dioxide is lost, extensive bromine substitution occurs, the products being dark glasses or stiff syrups. This seems to indicate polymerisation, which most probably involves free radicals. These products darken greatly when boiled with alkali, and no definite compounds have been isolated from them.

There is little evidence in group (4) that bromine reacts with one carboxyl group in preference to the other. Because of the absence of crystalline compounds in the reaction products from the unsymmetrically substituted acids, some of the lactone from the silver α-*iso*amylglutarate reaction was converted into the amide which, if pure, would be expected to crystallise readily. The fact that the product could not be induced to crystallise seems to indicate the presence of a mixture of amides, resulting from a mixture of lactones formed by the indiscriminate reaction of both carboxyl groups as follows (R = *iso*amyl):



Group (5). *Dibasic Aromatic Acids.*—Results are recorded in the table. In the case of *iso*phthalate the figures for the loss of carbon dioxide and for dibromide refer to the small amount of product and take no account of the fact that the great bulk of the silver salt is unchanged.

Group (5). *Dibasic Aromatic Acids.*

Silver salt.	Loss of CO_2, %.	Recovered acid, %.	Dibromide, %.	Unchanged silver salt, %.
Terephthalate	—	—	—	98·0
*iso*Phthalate	23·8	—	4·0?	78·4
Phthalate	38·4	29·0	10·1	0

With the phthalate, silver bromide is produced quantitatively, but the dark products of the reaction consist largely of unchanged acid; there is also evidence that some bromine substitution has occurred.

Experimental.

General.

(Yields are expressed as weights-%, unless otherwise stated, and were determined to the nearest mg.)

Preparation of Silver Salts.—The silver salts were prepared as described previously (Oldham and Ubbelohde, *loc. cit.*), except that AnalaR sodium carbonate was used instead of ammonia solution. Analyses were within about 1% of the calculated values.

Reaction with Bromine.—Reaction was carried out in a current of rigorously dried air, previously passed through concentrated sulphuric acid, phosphoric oxide, and again concentrated sulphuric acid. A concentrated sulphuric acid trap was placed at the exit. If these precautions are not taken, 50% or more of unchanged acid is recovered.

The apparatus consists of an U-tube, one limb of which is connected directly to the air supply, the other by means of a three-way adapter to a reflux condenser which in turn is connected to the terminal sulphuric acid trap. The second limb of the adapter carries a dropping funnel, while the third is used for the air stream, which can be passed either through the U-tube or directly into the adapter, by means of a T-piece provided with taps.

The silver salt is placed in the U-tube, through which air is passed for 1½ hours, maintained at 100° in a water-bath. (Precautions must be taken against the condensation of water round the joints

at the top of the U-tube.) The water-bath is then removed, and the air is caused to pass directly into the adapter by use of the appropriate taps on the T-piece. An excess over the calculated amount of a 15—18% solution of bromine in carbon tetrachloride (made up in bulk, and stored over phosphoric oxide) is added as quickly as possible through the dropping funnel, due regard being paid to the, sometimes vigorous, evolution of carbon dioxide. When the colour no longer fades, the red solution is warmed for a few minutes to ensure that the reaction is complete. Much longer boiling is sometimes necessary. The mixture is then filtered and the silver residues well washed with hot carbon tetrachloride.

Examination of the Silver Residue.—In quantitative work it is necessary to determine the amount of unchanged silver salt by extracting the silver residues with aqueous ammonia as already described (Oldham and Ubbelohde, *loc. cit.*). In the details given below the weight of silver salt recovered in this way has been allowed for.

Examination of the Product.—The filtered solution was evaporated on a water-bath and the residue usually dried *in vacuo* at 100°. In the case of the lower monobasic acids the carbon tetrachloride distillate contains the bulk of the bromo-compounds and these must be separated by distillation through a column. The procedure thereafter varied: various methods of separation were employed in each case, those recorded in the individual experiments being the most suitable. Sometimes the product was distilled; generally the neutral and the acid fraction of the product were separated by extraction three times from ether with aqueous sodium hydroxide. In the case of the higher fatty acids, alcohol must be added to this system which otherwise forms stable emulsions.

Any acids present are recovered by acidifying the alkaline extract with sulphuric acid, followed by extraction with ether; in the case of the dibasic acids it is advisable to determine any bromine in this water, since some bromo-acids produced during the reaction are decomposed by cold aqueous sodium hydroxide.

The neutral ethereal solution contains the bromides, any ester of the Simonini type, and, in the case of the dibasic acids, lactones. The product, after removal of the ether, was dried *in vacuo* at 100° and usually fractionally distilled. For the removal of lactones it was sometimes necessary to boil it with N/10-aqueous alcoholic sodium hydroxide.

Analyses.—The bromine content of the product was determined by the Stepanow method, except in the cases of the bromo-acids, for which titration with boiling N/10-alkali was usually sufficient. The carboxyl group was determined by titration with an excess of boiling N/10-alkali, followed by back-titration with N/10-nitric acid, and calculated as carbon dioxide.

Yields.—Yields quoted below for the crude products of the reaction are expressed as percentages of the weight of silver salt employed. Subsequent yields are calculated as percentages of the weight of crude product. The percentages of the theoretical yields have been given above in the tables and will not be repeated.

Details.

Group (1). *Aliphatic Monobasic Acids.—Special experiments with silver hexoate.* The two following experiments were designed to ascertain in what proportions bromine reacts with this salt. The quantities are expressed in g.-equivs. The calculation was complicated by the persistence of a trace of water, which gave rise to reaction (6) in which one equivalent of free parent acid is produced by one equivalent of bromine. The amount of acid present, determined by titration, must therefore be deducted from the original amount both of silver salt and of bromine. Any remaining bromine (determined by titration) or silver salt (determined as described above) must also be deducted from the original amounts. The amounts that remain then indicate the proportions in which the silver salt and the bromine have actually reacted. The determination of excess of bromine calls for no comment, but in determining the acid the carbon tetrachloride solution should be well shaken with excess of N/10-aqueous alkali, the carbon tetrachloride removed, and the excess of alkali back-titrated with acid.

(i) *Use of an excess of bromine.* $0{\cdot}485 \times 10^{-3}$ g.-equivs. of silver hexoate and 10^{-3} g.-equiv. of bromine gave $0{\cdot}076 \times 10^{-3}$ g.-equiv. of acid, $0{\cdot}105 \times 10^{-3}$ g.-equiv. remaining unchanged. Therefore the amount of silver salt used in the reaction was $0{\cdot}485 - 0{\cdot}076 = 0{\cdot}409 \times 10^{-3}$ g.-equiv. and that of bromine $1{\cdot}000 - 0{\cdot}076 - 0{\cdot}105 = 0{\cdot}819 \times 10^{-3}$ g.-equiv. These figures are in the proportion of 2 : 1 and indicate that reaction (5) has indeed taken place.

(ii) *Use of an excess of silver salt.* Silver hexoate (0·612) and bromine (1·00) produced acid (0·062) (all 10^{-3} g.-equiv.), $0{\cdot}081 \times 10^{-3}$ g.-equiv. of silver salt being recovered. Therefore the amount of silver salt used is $0{\cdot}612 - 0{\cdot}081 - 0{\cdot}062 = 0{\cdot}469$ and that of bromine used is $1{\cdot}000 - 0{\cdot}062 = 0{\cdot}938 \times 10^{-3}$ g.-equiv. These figures also are in the proportion of 2 : 1, showing that again reaction (5) has taken place.

Silver hexoate. The low yield (3·0%) shows that the bulk of the product has been removed with the carbon tetrachloride and must therefore be the bromide. Found: CO_2, 27·9% by cold titration, 31·2% by hot titration; Br, 5·8%. The cold titration corresponds to the presence of 73·6% of the free parent acid (Calc. for $C_6H_{12}O_2$: CO_2, 37·9%) and the difference between the two titrations probably indicates the presence of 13·9% of the Simonini ester (Calc. for $C_{11}H_{22}O_2$: CO_2, 23·6%). The bromine content corresponds to the presence of 10·9% of amyl bromide.

The carbon tetrachloride distillate was redistilled through a column till the temperature of the vapour reached 82°. The bromine content of the residual mixture of amyl bromide and carbon tetrachloride was 21·5%, corresponding to a 40·6% yield of amyl bromide, based on the original weight of silver salt. By calculation, a 60% yield would be expected, so presumably 33% of the product remained in the carbon tetrachloride.

Silver ββ-dimethylbutyrate. The bulk of the product (12·2% yield) consists of the bromide (Found: CO_2, 18·2% by cold titration, 21·5% by hot titration). The cold titration corresponds to the presence of 48·5% of free parent acid (Calc. for $C_6H_{12}O_2$: CO_2, 37·9%), while the difference between the two titrations probably represents 13·5% of Simonini ester (Calc. for $C_{11}H_{22}O_2$: CO_2, 23·6%). The remaining 38% of the product is undoubtedly the bromo-compound, but the bromine of neopentyl derivatives cannot be determined by ordinary methods. For this reason the carbon tetrachloride distillate was not further examined.

Silver diisoamylacetate. The yield of product was 74·6% (Found: CO_2, 3·1%), of which 11·6% was a solid acid (Found: CO_2, 22·1. Calc. for $C_{11}H_{22}O_2$: CO_2, 22·0%). The neutral fraction (81·2%) gave a distillate, b. p. 85—87°/2 mm. (yield 83·4%) (Found: CO_2, 0; Br, 35·2. Calc. for $C_{11}H_{23}Br$: Br, 34·0%). The yield of residue was 12·5% (Found: CO_2, 2·2; Br, 44·0. The CO_2 content may represent 17·7% of Simonini ester. Calc. for $C_{20}H_{38}O_2$: CO_2, 12·4%).

Silver stearate. The product (78·5%) (Found: CO_2, 0·9%) gave a solid acid fraction (5·8%) (Found: CO_2, 15·4%. Calc. for $C_{18}H_{36}O_2$: CO_2, 15·4%) and a neutral fraction (93·0%), m. p. 29—30° (Found: Br, 25·7. Calc. for $C_{17}H_{35}Br$: Br, 25·0%), the residue from the evaporation of the mother-liquors having m. p. 27·8—28·2° (Found: CO_2, 0; Br, 25·1%). The m. p. of 1-bromoheptadecane is 32°.

Silver cyclohexanecarboxylate. The product (65·9%, dried *in vacuo* at 60°) (Found: CO_2, 4·5%) gave a solid acid fraction (10·9%) (Found: CO_2, 34·0. Calc. for $C_7H_{12}O_2$: CO_2, 34·3%) and a neutral fraction (88·0%), which gave fractions, (i) b. p. 75—77°/2 mm. (57·3%) (Found: CO_2, 0; Br, 51·6. Calc. for $C_6H_{11}Br$: Br, 49·0%), and (ii) b. p. 70—80° (15·8%) (Found: CO_2, 6·7; Br, 31·8%). This corresponds to a mixture of 64·2% of *cyclo*hexyl bromide, calc. on the bromine, and 32·0% of the Simonini ester, calculated on the carbon dioxide values. Calc. for $C_{14}H_{24}O_2$: CO_2, 20·9%). The residue (4·4%) was a black tar. The loss in weight in this distillation is probably due to the volatility of *cyclo*hexyl bromide.

Group (2). *Aromatic Monobasic Acids.—Silver benzoate.* The yield of product (Found: CO_2, 20·1%) was 32·0%. As phenyl benzoate is very unstable to alkalis the ethereal solution of the product was extracted with aqueous potassium hydrogen carbonate and gave a crystalline acid fraction (27·2%) (Found: CO_2, 30·9. Calc. for $C_7H_6O_2$: CO_2, 36·0%). The low value for CO_2 indicates the presence of 14·2% of non-acidic material, probably phenol, which in turn would represent 30·1% of phenyl benzoate which has been hydrolysed even under these mild conditions. The neutral fraction (66·9%) was partly solid (Found: CO_2, 17·0%. This indicates the presence of 76·5% of phenyl benzoate. Calc. for $C_{13}H_{10}O_2$: CO_2, 22·2%), the rest being probably bromobenzene. The carbon tetrachloride distillate was distilled through a column till the temperature of the vapour reached 81°. The amount of carbon tetrachloride remaining in the residue was 8·3% (Found: Br, 46·7%) making the yield of bromobenzene 26·1% of the original silver benzoate.

Silver phenylacetate. The product (57·9%) (Found: CO_2, 7·9; Br, 30·5%) gave a solid acid fraction (14·4%) (Found: CO_2, 30·6. Calc. for $C_8H_8O_2$: CO_2, 32·3%) and a neutral fraction (81·0%), yielding fractions, (i) b. p. 73—80°/2 mm. (60·0%) (Found: CO_2, 0·8; Br, 44·9%. The CO_2 content indicates the presence of 4·1% of the Simonini ester. Calc. for $C_{11}H_{14}O_2$: CO_2, 19·4%. Calculation on the bromine content gives 96·1% of benzyl bromide. Calc. for C_7H_7Br: Br, 46·7%), and (ii) b. p. 80—130°/2 mm. (31·9%) (Found: CO_2, 9·6; Br, 23·2%. This corresponds to a mixture of 49·4% of the Simonini ester, calculated on the CO_2, and 49·9% of benzyl bromide, calculated on the bromine content). The loss in weight may be due to the volatility of benzyl bromide.

Silver o-nitrobenzoate. The product (70·4%) gave a solid acid fraction (9·3%) (Found: CO_2, 25·0. Calc. for $C_7H_5O_4N$: CO_2, 26·3%) and a crystalline neutral fraction (89·4%) (Found: CO_2, 2·6; Br, 32·9%). These figures correspond to a mixture of 83·0% of *o*-bromonitrobenzene (m. p. 41·5°) (Calc. for $C_6H_4O_2NBr$: Br, 39·6%) and 17·0% of the Simonini ester (Calc. for $C_{12}H_{14}O_4N_2$: CO_2, 15·2%). The substance softened at 32° and melted at 37—40°.

Group (3). *Aliphatic Monobasic Monoketo-acids.—Silver 9-ketodecane-1-carboxylate.* The product (72·1%) (Found: CO_2, 11·5; Br, 19·5%) was extracted from ether with sodium carbonate solution to give a largely solid acid fraction (47·3%) (Found: CO_2, 21·0; Br, 3·7%). This corresponds to a mixture of 87·1% of the free parent acid (Calc. for $C_{11}H_{20}O_3$: CO_2, 22·0%) with 12·9% of its monobromo-derivative (Calc. for $C_{11}H_{19}O_3Br$: CO_2, 15·7; Br, 28·6%), calculated from the bromine content; or 84·2 and 15·8% respectively calculated from the CO_2 content. For the neutral fraction (46·9%) (Found: CO_2, 2·5; Br, 30·7%) the bromine content corresponds to the presence of 90·3% of the bromo-compound (Calc. for $C_{20}H_{37}OBr$: Br, 34·0%).

Group (4). *Silver Salts of the Aliphatic Dibasic Acids.*—In this group, the acid fraction is usually a mixture of the free parent acid and bromo-acid. The composition of the mixture was calculated from the CO_2 content, and also from the bromine content. In all cases these agreed within 3%, and the average value is given below.

Sub-group A. (i) *Silver sebacate.* The yield of product was 61·3%. A further 0·9% was obtained by extracting the silver residues with acetone, and this material, crystallised from acetone, had m. p. 108—118° (Found: CO_2, 27·7; Br, 2·3%); the nature of this substance, more of which was obtained from the main fraction, remains obscure. The acid fraction (8·6%) (Found: CO_2, 16·2; Br, 31·7%), on treatment with light petroleum, gave 7·9% of a white crystalline substance, m. p. 118—120° (Found: CO_2, 33·7; Br, 0%). This was doubtless the same as the product from the acetone extract described above. An oil (91·7%) obtained on removal of the light petroleum was dissolved in ether and again extracted with aqueous sodium hydroxide; 8·7% was obtained from the ether and was added to the main neutral fraction; 86·1% of an acid product was isolated which crystallised (m. p. 31—33°) and was so soluble in all solvents that recrystallisation was unsatisfactory (Found: CO_2, 17·2; Br, 21·8%. Calc. for 9-bromopelargonic acid (m. p. 36—36·5°), $C_9H_{17}O_2Br$: CO_2, 18·5; Br, 33·7%). The neutral fraction (90·2%) gave a distillate (94·8%), b. p. 140°/5 mm. (Found: CO_2, 0; Br, 59·3. Calc. for $C_9H_{18}Br_2$: Br, 58·8%). The dark residue (4·7%) (Found: CO_2, 5·7; Br, 44·5%) was not further examined. The products of the reaction contained 85·4% of the dibromide, 6·7% of the bromo-acid, 2·1% of an unknown crystalline acid, and 4·2% of a dark residue.

The distillate was treated with sodium phenoxide as described by Ssolonina (*Zentr.*, 1899, I, 26), giving a 99% yield of the diphenoxy-derivative, m. p. (after recrystallisation from absolute alcohol) 84—86° (lit., 83—84°), while 8·1% of impure crystals, m. p. 44—51°, were obtained from the mother-liquors.

(ii) *Silver azelaate.* The product (64·2%) gave an acid fraction (8·0%) (Found: CO_2, 26·7; Br, 25·6%). This corresponds to a mixture of 72·8% of the bromo-acid (Calc. for $C_9H_{15}O_3Br$: CO_2, 19·7; Br, 28·8%) and 27·2% of azelaic acid (Calc. for $C_9H_{16}O_4$: CO_2, 46·8%) and a neutral fraction (91·7%) which gave a distillate (89·9%), b. p. 125°/2 mm. (Found: CO_2, 0; Br, 61·0. Calc. for $C_7H_{14}Br_2$:

Br, 62·0%). The residue (7·3%) was not further investigated. The products contained 82·4% of the dibromide, 5·8% of the bromo-acid, and 2·2% of azelaic acid.

(iii) *Silver pimelate.* The product (59·3%) (Found: CO_2, 8·6%) gave an acid fraction (19·2%) [Found: CO_2, 24·3; Br, 37·7. This corresponds to a mixture of 92·9% of the bromo-acid (Calc. for $C_8H_{11}O_2Br$: CO_2, 22·5. Br, 41·0%) and 7·1% of pimelic acid (Calc. for $C_7H_{12}O_4$: CO_2, 55·0%)]. The neutral fraction (72·2%) gave a distillate, b. p. 120°/2 mm. (63·4%) (Found: CO_2, 0; Br, 71·5. Mainly $C_8H_{16}Br_2$: Calc., Br, 69·9%). The residue (35·5%) was boiled with aqueous alcoholic sodium hydroxide but no very clear-cut results were obtained; the isolation of 8·5% of a neutral substance would seem to indicate the presence of a compound of the type of a Simonini ester, formed by the unsymmetrical loss of two molecules of CO_2 between two molecules of pimelic acid, such as . The product of the reaction contained 45·8% of the dibromide, 17·8% of the dibromo-acid, 1·4% of free parent acid, and 25·6% of an unknown substance which is being further investigated.

Sub-group B. (i) *Silver α-isoamyladipate.* The product (54·2%) (Found: CO_2, 13·5%) gave a distillate, b. p. 115—130°/2 mm. (44·1%). The CO_2 content (2·0%) corresponds to the presence of 7·4% of the lactone (Calc. for $C_{10}H_{18}O_2$: CO_2, 25·8%); allowing for this, the bromine content (53·9%) is revalued at 58·3%, showing that the substance is mostly the dibromide (Calc. for $C_9H_{14}Br_2$: Br, 55·8%). The residue (53·0%) (Found: CO_2, 21·7. Br, 17·6%) corresponds to a mixture of 55·3% of the bromo-acid) (Calc. for $C_{10}H_{19}O_2Br$: CO_2, 17·5; Br, 31·8%), 41·7% of the lactone, and 3% of isoamyladipic acid (Calc. for $C_{11}H_{20}O_4$: CO_2, 40·7%). In this case also the residue was boiled with excess of alkali, giving results similar to those described for pimelic acid; the isolation of 13·2% of a neutral substance indicates the presence of a compound of the Simonini ester type. The reaction products contained 40·7% of the dibromide, 29·3% of the bromo-acid, 1·6% of isoamyladipic acid, and 22·1% of lactone + Simonini-like compound. This is being further investigated.

(ii) *Silver adipate.* (*a*) The yield obtained in carbon tetrachloride was 29·5% (Found: CO_2, 16·4%). The silver residues were extracted with hot acetone, giving a further 11·9% of crystalline product (cf. p. 103) (Found: CO_2, 55·3%), softening at 136°, m. p. 141—146°, unchanged on admixture with adipic acid. As it remained impure after recrystallisation from glacial acetic acid, it was converted into the ethyl ester and distilled (88·5% yield) (Found: CO_2, 43·6. Calc. for $C_{10}H_{18}O_4$: CO_2, 43·5%). The residue was a dark gum. The ester was hydrolysed to adipic acid (99·5%) (Found: CO_2, 59·2. Calc. for $C_6H_{10}O_4$: CO_2, 60·2%), m. p. 151—153°, unchanged on mixing with adipic acid. Allowance being made for this amount of adipic acid, the yield of other products in the carbon tetrachloride extract is 40·1%.

Although the neutral portion of the usual alkaline extraction could be isolated without difficulty, it proved impossible to isolate the acid portion in good yield. The amount of bromo-acid present was determined by boiling the strongly alkaline extract for ½ hour and determining the bromine content. This was equivalent to the presence of 5·7% of the bromo-acid in the original carbon tetrachloride extract.

(*b*) The crude product from the carbon tetrachloride was heated in a sealed tube for 2 hours at 100° with four times the theoretical amount of hydrogen bromide in glacial acetic acid and an excess of acetic anhydride to destroy any water present; the product was evaporated to dryness *in vacuo* at 100°. As the dibromide is considerably volatile under these conditions, the total distillate was flooded with water, neutralised with sodium carbonate, and extracted with ether, comparatively large quantities of the dibromide being recovered. The total yield of product was 130·4%. The alkaline extract thereof (all solutions were kept ice-cold) was immediately run into ice-cold acid. The acid fraction (52·1%) (Found: CO_2, 25·8; Br, 44·3. Calc. for $C_8H_{13}O_2Br$: CO_2, 24·3; Br, 44·2%) failed to crystallise, and its subsequent identification is described below. The neutral fraction (45·2%) gave a distillate (71·8%), b. p. 80—90°/5 mm. Analysis (CO_2, 13·3; Br, 5·4%) of the residue (24·2%) might indicate presence of 4-bromobutyl δ-bromovalerate (Calc. for $C_9H_{16}O_2Br_2$: CO_2, 13·6; Br, 50·0%); this substance would easily have distilled under the conditions employed. As this material represented only 12—15% of the reaction product, it was not further investigated. The bulked distillates from several experiments were redistilled (yield 93·7%), b. p. 75—85°/5 mm. (Found: CO_2, 0; Br, 71·3. Calc. for $C_4H_8Br_2$: Br, 74·0%), a residue (3·3%) (Found: Br, 31·0%) not being further investigated.

The products of the reaction contained 31·1% of the dibromide, 28·7% of adipic acid, 22·8% of the lactone, 4·0% of the bromo-acid, and 10·1% of unidentified material. If the carbon tetrachloride extract only is considered, these figures become 42·3, 32·0, 5·7, and 14·2%, respectively.

The distillate was converted into 1 : 4-diphenoxybutane as described above (yield 92·0% of theory). Recrystallisation from absolute alcohol yielded crystals, m. p. 99—100° (lit., 99°). The mother-liquors yielded 15·0% of material, m. p. 30—40°.

The bromo-acid was heated with twice its volume of thionyl chloride on a water-bath, and then treated cautiously with a small quantity of alcohol, evaporated to dryness *in vacuo* at 100° (yield 99·3%) (Found: CO_2, 22·9; Br, 33·7. Calc. for $C_7H_{11}O_2Br$: CO_2, 22·1; Br, 34·2%), and distilled (distillate: 71·7%; b. p. 100—105°/5 mm.; residue: 7·6% of a black tar). As treatment of the ester with sodium phenoxide in alcohol gave a very poor yield of the acid (presumably owing to the formation of δ-valerolactone), it was boiled in acetone with the acetone compound of sodium phenoxide (Segaller, *J.*, 1914, **105**, 112). Two treatments with this reagent removed the bromine completely. In this case hydrolysis also occurred, the acid, and no δ-valerolactone being formed. Ethyl δ-phenoxyvalerate (59·9% of theory) (Found: CO_2, 18·9; Br, 0. Calc. for $C_{13}H_{18}O_3$: CO_2, 19·8%) was isolated by removing the acetone on a water-bath, shaking the residue with water–ether, and washing the ethereal layer with sodium hydroxide solution. This was hydrolysed with aqueous-alcoholic sodium hydroxide and, as the solution became cloudy on removal of the alcohol, it was extracted with ether, from which 5·2% of a neutral crystalline compound was obtained in insufficient quantity for further work. The solution was then acidified and extracted with ether, yielding 96·1% of the calculated amount of δ-phenoxyvaleric acid (after allowance for the neutral substance mentioned above), m. p. 62—63°.

The substance was too soluble in all solvents to be satisfactorily recrystallised, but on being pressed between filter paper had m. p. 63—65° (lit., 66°) (Found : CO_2, 21·9. Calc. for $C_{11}H_{14}O_4$: CO_2, 22·6%). More acid (impure) was recovered from the alkaline washings from the ester ; these were bulked, acidified, neutralised with potassium hydrogen carbonate solution, extracted 3 times with ether to remove phenol, again acidified, and extracted with ether. The yield of impure dark acid was 32·4%, making the total yield 93·3% of theory (Found : CO_2, 20·8%).

The bromo-ester was treated with excess of ethyl sodiomalonate, hydrolysed by alkali, decarboxylated at 180—200°, and dried *in vacuo* at 100°. This gave 81·0% of pimelic acid, m. p. 101—104° (after recrystallisation from benzene) (Found : CO_2, 53·4. Calc. for $C_7H_{12}O_4$: CO_2, 55·0%), unchanged on mixing with an authentic specimen. The mother-liquors yielded 36·0% of impure product. The somewhat unsatisfactory yield of pimelic acid is a feature common to many decarboxylations of malonic derivatives.

Sub-group C. (i) *Silver γ-isoamylglutarate.* The product (45·9%) (Found : CO_2, 19·0 ; Br, 24·6%) gave a distillate, b. p. 110—120°/2 mm. (67·9%) (Found : CO_2, 2·3% by cold titration, 17·6% by hot titration ; titratable Br, 4·2% ; total Br, 25·1%). The bromine content by titration agrees with the CO_2 content by cold titration to indicate the presence of 12·4% of the bromo-acid (Calc. for $C_9H_{17}O_3Br$: CO_2, 18·3 ; Br, 33·7%). The remaining 15·3% of CO_2 corresponds to 34·2% of the lactone (Calc. for $C_9H_{16}O_2$: CO_2, 28·2%). With allowance for these factors the bromine content of the remainder is revalued at 62·7% (Calc. for $C_9H_{16}Br_2$: Br, 58·8%). Analysis (CO_2, 26·6 ; Br, 16·8%) of the residue (29·1%) corresponds to a mixture of 49·9% of the bromo-acid, 26·6% of the lactone, and 23·6% of α-isoamylglutaric acid (Calc. for $C_{10}H_{18}O_4$: CO_2, 43·5%). To confirm this the residue was boiled with excess of alkali, whereupon it gave 11·8% of a neutral substance, which was not further examined, 16·8% of bromine, and 69·4% of an acid (Found : CO_2, 32·6%), corresponding to a mixture of 71·3% of the lactone and 28·7% of isoamylglutaric acid. The expected amount of α-isoamylglutaric acid was only 11·8%, but the neutral material could correspond to a further 15·9% of this acid. The reaction products consisted of 22·6% of the dibromide, 22·9% of the bromo-acid, 49·5% of the lactone, and 2·8% of isoamylglutaric acid.

(ii) *Silver ββ-dimethylglutarate.* The product (29·2%) (Found : CO_2, 28·4 ; Br, 15·1%) was boiled with a slight excess of N/10-aqueous-alcoholic sodium hydroxide, giving a neutral fraction (21·6%) (Found : CO_2, 1·4 ; Br, 65·7%), the CO_2 content of which corresponds to the presence of 3·6% of the lactone (Calc. for $C_6H_{10}O_2$: CO_2, 38·5%). With allowance for this, the bromine content of the remainder becomes 68·2% (Calc. for $C_7H_{12}Br_2$: Br, 69·9%). The acid fraction (61·5%) [Found : CO_2, 39·4%. The aqueous portion contained 11·4% of bromine which corresponds to 27·8% of the bromo-acid (Calc. for $C_7H_{11}O_3Br$: CO_2, 22·5 ; Br, 41·0%)] gave a distillate, b. p. 80°/2 mm. (84·5%) (Found : CO_2, 38·4%). In spite of its good analysis the distillate crystallised badly, and a cold titration showed CO_2, 1·2%. The *residue* was 11·2% (Found : CO_2, 52·5. Calc. for ββ-dimethylglutaric acid, $C_7H_{12}O_4$: CO_2, 55·0%). The reaction products consisted of 20·8% of the dibromide, 27·8% of the bromo-acid, 36·5% of the lactone, and 6·8% of ββ-dimethylglutaric acid.

(iii) *Silver α-methylglutarate.* The product (31·7%) (Found : CO_2, 38·5%) gave a distillate, b. p. 65—80°/2 mm. (76·3%) (Found : CO_2, 36·7 ; Br, 12·0%. This corresponds to a mixture of 83·6% of the lactone (Calc. for $C_5H_8O_2$: CO_2, 44·0%) and 16·4% of the bromo-compound (Calc. for $C_5H_9Br_2$: Br, 74·0%). The bromine content (17·7%) of the residue (21·7%) (Found : CO_2, 34·6%) indicates the presence of 40% of the bromo-acid (Calc. for $C_5H_9O_2Br$: CO_2, 24·3 ; Br, 44·2%) with 60% of the lactone, but such a mixture would require CO_2, 36·1%. The reaction products consisted of 12·5% of the dibromide, 8·2% of the bromo-acid, and 79·1% of the lactone.

(iv) *Silver glutarate.* There was no evidence of the presence of trimethylene bromide. The product (24·4%) gave a distillate, b. p. 70—80°/2 mm. (54·0%) (Found : CO_2, 44·4 ; Br, 10·9%). These values indicate a mixture of 83·6% of the lactone (Calc. for $C_5H_8O_2$: CO_2, 51·1%) and 16·4% of the dibromide (Calc. for $C_5H_8Br_2$: Br, 79·2%). They do not agree so well with any mixture containing the bromo-acid. The residue (36·4%) (Found : CO_2, 52·2 ; Br, 0%) is a mixture of the lactone and 7·0% of glutaric acid (Calc. for $C_5H_8O_4$: CO_2, 66·6%). The reaction product consisted of 7·2% of the dibromide, 70·6% of the lactone, and 2·6% of glutaric acid. The deficiency shown by these figures is possibly due to the loss of the volatile dibromide.

Sub-group D. (i) *Silver isoamylsuccinate.* The product (50·7%) (Found : CO_2, 13·7 ; Br, 35·0%) gave a neutral fraction (71·0%) (Found : CO_2, 7·1 ; Br, 44·6%), b. p. 85—95°/2 mm. (63·7%) (Found : CO_2, 4·3 ; Br, 55·4%), and a residue (35·0%) (Found : CO_2, 11·0 ; Br, 26·6%), presumably consisting of products of the Simonini-ester type. The CO_2 content of the distillate indicated the presence of an ester, a lactone being impossible. The distillate was therefore boiled with aqueous-alcoholic N/10-sodium hydroxide, to give 70·2% of a neutral material [Found : CO_2, 0·8 ; Br, 61·0. Mostly dibromide (Calc. for $C_9H_{18}Br_2$: Br, 62·0%)] and 12·1% of an acid (Found : CO_2, 24·5%). The residual aqueous solution contained 6·5% of bromine. The CO_2 content of the acid could correspond to that required by a dihydroxy-acid (Calc. for $C_9H_{18}O_4$: CO_2, 25·0%). To confirm this it was treated with silver oxide and ethyl iodide, but it gained only 11·2% in weight. The CO_2 content however proved to be 17·3% which is close to that required by the ethyl ester of a diethoxy-acid (Calc. for $C_{13}H_{26}O_4$: CO_2, 16·9%). The acid fraction (26·9%) (Found : CO_2, 24·1 ; Br, 17·7%) was a complex mixture from which no definite product could be isolated. The products of the reaction contained 31·7% of the dibromo-compound.

(ii) *Silver methylsuccinate.* No dibromide could be found in the carbon tetrachloride distillate. The product (28·5%) (Found : CO_2, 20·5%) gave a neutral fraction (60·0%) (Found : CO_2, 14·5 ; Br, 37·3%), b. p. 110—115°/2 mm. (58·3%) (Found : CO_2, 7·9 ; Br, 58·8%), probably mostly the dibromide (Calc. for $C_5H_8Br_2$: Br, 79·2%) mixed with an acidic substance of similar nature to that obtained from silver isoamylsuccinate. The residue (40·0%) (Found : CO_2, 17·7 ; Br, 50·1%) was not further investigated. The acid fraction (36·5%) was a complex mixture from which no definite product could be isolated. The reaction products contained a maximum of 26·0% of the dibromo-compound, which would be lowered if the ester in the neutral fraction itself contained bromine. The rest of the product was indefinite.

(iii) *Silver succinate.* The reaction mixture required 1½ hours' boiling. Fractionation of the carbon tetrachloride disclosed no ethylene dibromide. Dissolution of the product (20·2% yield) (Found: CO_2, 45·9%) in ether gave 37·7% of succinic acid (Found: CO_2, 74·6. Calc. for $C_4H_6O_4$: CO_2, 74·5%). The material (61·0%) (Found: CO_2, 32·8; Br, 39·1%) from the ethereal solution was again dissolved in ether, the solution was washed 3 times with water, and the washings were extracted with ether. Titration of the water showed CO_2, 40·3. 89% of material (Found: CO_2, 30·9; Br, 43·1%) was recovered from the ether. The bromine content corresponds to the presence of 82·5% of the bromo-acid (Calc. for $C_3H_5O_2Br$: CO_2, 28·7; Br, 52·2%), and 17·5% of a substance containing CO_2, 41·1%. The nature of the latter, as of the substance in the water, remains obscure. The reaction product contains 44·8% of bromo-acid, and 37·7% of succinic acid.

Sub-group E. (i) *Silver benzylmalonate.* The reaction mixture was boiled for ½ hour, and the silver residue well washed with hot carbon tetrachloride and then hot acetone. The carbon tetrachloride solution yielded 14·9% of a stiff syrup (Found: CO_2, 21·1; titratable Br, 31·6%). The yield of product from the acetone was 64·2% (Found: CO_2, 24·6°; titratable Br, 27·4; total Br, 38·1%); it was a glass, insoluble in ether. The analysis shows that only 12·0% of "CO_2" content had been lost, and that extensive bromination had occurred, some of the bromine having apparently even entered the ring. Treatment with alkali caused great darkening, even in the cold, and nothing but dark syrups or glasses could be isolated.

Group (5). *Aromatic Dibasic Acids.—Silver terephthalate.* The reaction mixture was boiled for 3 hours with occasional addition of more bromine. Examination of the silver residues by standard methods showed the presence of only 2·0% of silver bromide, 98·0% of the silver salt being recovered unchanged. Analysis of the product (5·8%) showed CO_2, 19·2%. Bromobenzoic acid $C_7H_5O_2Br$ requires CO_2, 21·8%, but as the product did not crystallise there can have been none of this acid present. There was too little product for further investigation.

Silver isophthalate. The mixture was boiled for 3 hours. The silver residues were extracted with hot acetone in addition to carbon tetrachloride. The yield from both extracts was 13·6% (Found: CO_2, 26·8%). The neutral fraction (18·3%) was not further examined, but was probably the dibromide. The acid fraction (80·3%) (Found: CO_2, 36·0%), m. p. >300°, was boiled with benzene, in which *iso*phthalic acid is insoluble, and filtered. The crystalline residue (Found: CO_2, 52·0. Calc. for $C_8H_6O_4$: CO_2, 53·0%), was not further examined. Analysis of the silver residues indicated the presence of 21·6% of silver bromide, showing that 78·4% of the salt was unchanged. The reaction products appeared to consist of 37·7% of isophthalic acid and 15·7% of a neutral substance, probably the dibromide, the rest of the product being unidentified.

Silver phthalate. The mixture was boiled for ½ hour. The carbon tetrachloride gave 34·7% of material (Found: CO_2, 25·7%). A further 12·6% were obtained by extracting the silver residues with hot acetone (Found: CO_2, 44·9%), this being dark and having m. p. 190—200°, unchanged by admixture with phthalic acid (Calc. for $C_8H_6O_4$: CO_2, 53·0%). The main product was extracted from ether with aqueous sodium hydroxide, leaving a neutral fraction (18·2%) (Found: CO_2, 0; Br, 62·6. Calc. for $C_6H_4Br_2$: Br, 68·3%). The dark acid fraction (80·9%) (Found: CO_2, 30·9%) was purified by treatment with silver oxide and ethyl iodide, to give an ester, b. p. 155—170°/2 mm. (88·7%) (Found: CO_2, 26·3; Br, 12·9%). The residual black tar was not further examined. The distillate was hydrolysed and the acidified solution (*A*) extracted with chloroform, in which phthalic acid is insoluble; the yield of partly crystalline product was 27·7% (Found: CO_2, 15·7%). Dibromobenzoic acid (Calc. for $C_7H_4O_2Br_2$: CO_2, 15·1%) is a strongly crystalline substance. Further extraction of (*A*) with ether yielded an oil (49·1%) (Found: CO_2, 39·9%), which when rubbed with chloroform afforded phthalic acid (m. p. and mixed m. p.); 62·4% of the ether-extracted material was recovered from the chloroform mother-liquors (Found: CO_2, 27·3%). This reaction gave 13·3% of the dibromide, 26·8% of phthalic acid, and a number of unidentified acidic products.

Note on the Purity of the Acids used.—Azelaic acid was made from Kahlbaum's monomethyl azelaate; stearic and palmitic acids were Kahlbaum's and Schuchardt's respectively. The following were pure commercial products: hexoic, benzoic, nitrobenzoic, phenylacetic, phthalic, isophthalic, terephthalic, adipic, and succinic acid. The sebacic acid, being coloured, was recrystallised once from glacial acetic acid. The keto-acids were made by Ruzicka and Stoll's method (*Helv. Chim. Acta*, 1927, **10**, 691). The other acids were made from ethyl malonate.

γ-iso-Amyladipic acid. Ethyl sodiomalonate was treated successively with ethyl γ-bromobutyrate (from ethyl sodiomalonate and 2-phenoxyethyl bromide) and isoamyl bromide, and the product then hydrolysed, decarboxylated, and purified by re-esterification and distillation (Found: CO_2, 40·8. Calc. for $C_{11}H_{20}O_4$: CO_2, 40·7%); it had m. p. 66—68° and gave a silver salt (Found: Ag, 50·1. Calc. for $C_{11}H_{14}O_4Ag_2$: Ag, 50·2%).

α-iso-Amylglutaric acid. Ethyl sodiomalonate was treated successively with ethyl β-bromopropionate and isoamyl bromide; the product, isolated as above, failed to crystallise, even on long storage (Found: CO_2, 43·4. Calc. for $C_{10}H_{18}O_4$: CO_2, 43·5%). The silver salt was also analysed (Found: Ag, 51·0. Calc. for $C_{10}H_{14}O_4Ag_2$: Ag, 51·9%).

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23. *Chemotherapeutic Diamidines. The Sulphur Analogue of 4 : 4′-Diamidinostilbene.*

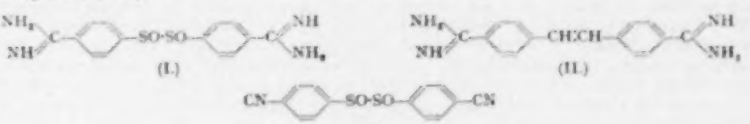
By Ludwig Bauer and J. Cymerman.

Preparation of di-*p*-cyanophenyl disulphoxide (III) is described. Attempts to synthesise di-*p*-amidinophenyl disulphoxide (I), a sulphur analogue of 4 : 4′-diamidinostilbene, by interaction of (III) with ammonium thiocyanate, ammonium benzenesulphonate, and ammonium benzenesulphonate and ammonia gave, in every case, di-*p*-amidinophenyl disulphide, which has been prepared also by interaction of di-*p*-cyanophenyl disulphide with ammonium thiocyanate and by the Pinner method by way of the 4 : 4′-*di*(*carboxyimino ethyl ether*) *dihydrochloride*. Application of the Pinner method to (III) gave its 4 : 4′-*di*(*carboxyimino ethyl ether*) but alcoholic ammonia yielded only the disulphide diamidine. Reaction mechanisms are discussed. Heating the di-imino diethyl ether dihydrochlorides afforded the corresponding diamides; 4 : 4′-*di*-(p-*N*-*phenylamidinophenyl*) *disulphide dibenzenesulphonate* was prepared, but attempted preparation of the disulphoxide analogue from (III) gave a deep-blue compound of unknown structure. Ultra-violet absorption spectra of aromatic disulphides and disulphoxides have been determined.

The chemotherapeutic properties of diamidines are well known (Lourie and Yorke, *Ann. Trop. Med. Parasit.*, 1937, **31**, 435; 1939, **33**, 289; King, Lourie, and Yorke, *Lancet*, 1937, **233**, 136), the aromatic diamidines, in particular, showing pronounced antibacterial activity (Ashley, Barber, Ewins, Newbery and Self, *J.*, 1942, 103; Wien, *Brit. J. Pharmacol.*, 1948, **3**, 211). Replacement of carbon by sulphur in many organic compounds of biological interest has yielded sulphur analogues of lower toxicity and equal or increased activity (Steinkopf and Ohse, *Annalen*, 1924, **437**, 14; 1926, **448**, 205; Warren, Marsh, Thompson, Shelton, and Becker, *J. Pharm. Exp. Therap.*, 1943, **79**, 187; Dann and Moller, *Ber.*, 1947, **80**, 23) and it was thus of interest to attempt the synthesis of di-*p*-amidinophenyl disulphoxide (I), a sulphur analogue of 4 : 4′-diamidinostilbene (II) which has outstanding trypanocidal activity (Ashley *et al.*, *loc. cit.*).

The required starting material, di-*p*-cyanophenyl disulphoxide (III), was obtained by Cymerman, Koebner, and Short (*J.*, 1948, 381) in low yield as a by-product in the preparation of *p*-cyanobenzenesulphinic acid. Its attempted preparation from the sulphinic acid at 80—90° in the presence of hydriodic acid and sulphur dioxide (Otto, *Ber.*, 1882, **15**, 121; Smiles and Gibson, *J.*, 1924, 180; von Braun and Weissbach, *Ber.*, 1930, **63**, 2836; Hilditch, *J.*, 1910, 1096) gave only an acidic hydrolysis product, presumably di-*p*-carboxyphenyl disulphoxide, in 90% yield, while the action of concentrated hydrochloric acid on the sulphinic acid at 25° for 3 days yielded the disulphoxide (55%) accompanied by the corresponding diamide. However, hydrochloric acid at 0° during 2—3 days readily afforded 70% of pure (III); the mother-liquors contained *p*-cyanobenzenesulphonic acid, isolated as the p-*toluidine* salt in 45% yield, in agreement with the accepted mechanism (1) for the formation of disulphoxides from the sulphinic acids (Otto, *Ber.*, 1876, **9**, 1639; Pauly and Otto, *ibid.*, 1877, **10**, 2181; 1878, **11**, 2070, 2073; von Braun and Weissbach, *loc. cit.*).

Synthetic methods available for the preparation of the required diamidine included the well-known Pinner synthesis (Pinner, *Ber.*, 1877, **10**, 1889; cf. Derby, *Amer. Chem. J.*, 1908, **39**, 437) through the imino-ether, and the recently-developed fusion methods using ammonium salts such as the benzenesulphonate (Oxley and Short, *J.*, 1946, 147) and thiocyanate (Partridge and Short, *J.*, 1947, 390).



(I.) (II.) (III.)

$$3R{\cdot}SO_2H \longrightarrow R{\cdot}SO_2{\cdot}SR + R{\cdot}SO_2{\cdot}OH + H_2O \quad . \quad . \quad . \quad . \quad (1)$$

Interaction of the disulphoxide (III) with ammonium thiocyanate at 180° (method *A*) gave a solid diamidine showing an intense colour in the Fuller reaction (Fuller, *Nature*, 1944, **154**, 773), and affording an 82·5% yield of a *dihydrochloride hemihydrate* (m. p. 316°) and from this an anhydrous *salt* (m. p. 310—311°) which gave analytical figures corresponding to di-*p*-amidinophenyl disulphide dihydrochloride. Further confirmation of the nature of the product was afforded by the preparation of the *dibenzenesulphonate*, *dipicrate*, and *dibenzoate dihydrate*.

This diamidine has been reported by Ashley *et al.* (*loc. cit.*) who obtained it by the Pinner

synthesis from di-*p*-cyanophenyl disulphide and report m. p. >300° for the dihydrochloride dihydrate. In our hands the action of alcoholic hydrogen chloride on di-*p*-cyanophenyl disulphide (Bauer and Cymerman, *J.*, in the press) gave (method *D*) (*diphenyl disulphide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *dihydrochloride* in quantitative yield, and dry alcoholic ammonia converted this into the diamidine which gave a dibenzenesulphonate (53% yield) and dihydrochloride identical with those obtained from method *A*.

In order to examine the validity of the ammonium thiocyanate method in this case, interaction of di-*p*-cyanophenyl disulphide with this reagent was investigated (method *E*) and found to give the expected dibenzenesulphonate (35% yield), identical with that obtained from method *A*.

Attention was then turned to the alternative method of preparation using ammonium benzenesulphonate in the presence of ammonia gas (Oxley, Partridge, and Short, *J.*, 1948, 303). By this method the disulphoxide (III) at 180° (method *B*) afforded 51% of the dihydrochloride obtained in method *A*.

Finally, fusion of the disulphoxide (III) with ammonium benzenesulphonate alone at 250—255° (method *C*) yielded 81% of the dibenzenesulphonate identical with that obtained by method *A*. The aqueous mother-liquors afforded benzamidine-*p*-sulphonic acid (m. p. >360°) giving an intense amidine test (Fuller), completely soluble in sodium hydroxide solution (20%), and precipitated from this solution by hydrochloric acid (cf. Remsen and Muckenfuss, *Amer. Chem. J.*, 1896, **18**, 354). Disulphoxides are often regarded as reacting as the "thiolsulphonates" $R{\cdot}SO_2{\cdot}S{\cdot}R$ rather than as the symmetrical disulphoxides $R{\cdot}SO{\cdot}SO{\cdot}R$ (Gibson, Miller, and Smiles, *J.*, 1925, 1821; Gilman, Smith, and Parker, *J. Amer. Chem. Soc.*, 1925, **47**, 851; cf. however Fromm and Palma, *Ber.*, 1906, **39**, 3508; Hinsberg, *Ber.*, 1908, **41**, 2836, 4294; 1909, **42**, 1278). They are hydrolysed by alkali to a mixture of the disulphide and sulphinic acid (cf., *inter alia*, Pauly and Otto, *loc. cit.*; Bulmer and Mann, *J.*, 1945, 683); this has been variously postulated to proceed through the thiol (Otto and Rossing, *loc. cit.*), by hydrolytic fission (Zincke and Farr, *Annalen*, 1912, **391**, 58), through the sulphenic acid (Fromm, *loc. cit.*; Zincke, *Annalen*, 1914, **406**, 103), or by an oxidation–reduction mechanism (Zincke and Farr, *loc. cit.*), the overall reaction in every case being :

$$3R{\cdot}SO_2{\cdot}SR + 2H_2O \longrightarrow 4R{\cdot}SO_2H + RS{\cdot}SR \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The yields of di-*p*-amidinophenyl disulphide obtained by methods *A*, *B*, and *C*, however, all greatly exceed the theoretical figure calculated from reaction (2). It was shown by Halssig (*J. pr. Chem.*, 1897, **56**, 213) that the formation of disulphide and sulphonic acid from a sulphinic acid takes place, not only in an acidic environment, but also readily on warming the mixture in the presence of ammonia or by the action of heat on an ammonium sulphinate, according to reaction (1). Under the experimental conditions used, reactions (1) and (2) are thus consecutive and complementary, the net equation being (3) :

$$5R{\cdot}SO_2{\cdot}SR + 2H_2O \longrightarrow 3RS{\cdot}SR + 4R{\cdot}SO_2{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The expression (3) accounts satisfactorily for both the nature and the quantities of the two products obtained in methods *B* and *C*. The yields of diamidine obtained by method *A*, however, still exceed the theoretical amounts calculated from equation (3).

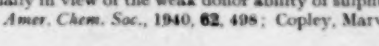
Disulphoxides are readily reduced to the corresponding disulphides by a variety of mild reducing agents (Hinsberg, *loc. cit.*; Smiles and Gibson, *loc. cit.*; Miller and Smiles, *J.*, 1925, 224) according to reaction (4); since ammonium thiocyanate, which at the reaction temperature (180°) exists as a mixture of thiourea, ammonia, hydrogen sulphide, and thiocyanic acid (Reynolds and Werner, *J.*, 1903, 1; Atkins and Werner, *J.*, 1912, 1172; Krall, *J.*, 1913, 1379), would be expected to possess reducing properties, direct reduction to the disulphide probably occurs during the reaction in method (*A*), the net reaction (5) being, in this case, a summation of (3) and (4). Calculation on this basis shows excellent agreement between the theoretical and experimental yields in method *A*.

$$2R{\cdot}SO_2{\cdot}SR + H_2 \longrightarrow 2R{\cdot}SO_2H + RS{\cdot}SR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$4R{\cdot}SO_2{\cdot}SR + 3H_2 \longrightarrow 3RS{\cdot}SR + 2R{\cdot}SO_2{\cdot}OH + 2H_2O \quad . \quad . \quad . \quad . \quad (5)$$

Since it had so far proved impossible to obtain the desired compound (I), the Pinner method was next applied to di-*p*-cyanophenyl disulphoxide (method *F*). Reaction with alcoholic hydrogen chloride readily afforded a theoretical yield of (*diphenyl disulphoxide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *dihydrochloride* (V) and from this the crystalline *hemihydrate* of the free base. With ethanolic ammonia the imino-ether hydrochloride gave quantitatively the diamidine dihydrochloride obtained by method *A*. The extremely ready conversion of disulphoxides in

alkaline solution into the disulphides and sulphinic acids (equation 1) has been noted by many workers (cf. Kharasch, Potempa, and Wehrmeister, *Chem. Reviews*, 1946, **39**, 328; Otto and Rossing, *loc. cit.*), as has their contrasting stability in acid (Zincke and Eismayer, *Ber.*, 1918, **51**, 751). After treatment with dry ammonia in ethanol at room temperature the disulphoxide (III) was recovered quantitatively even after two weeks, but interaction in ethylene glycol at 180° afforded, as sole product, 56% (calculated from equation 3) of di-*p*-cyanophenyl disulphide. The ready conversion of the imino-ether hydrochloride (IV) into the disulphide is thus surprising and must be occasioned by the labilising effect of the cationic iminium group on the thiol-sulphinate system in (IV), especially in view of the weak donor ability of sulphur compared with oxygen (Gordy and Stanford, *J. Amer. Chem. Soc.*, 1940, **62**, 498; Copley, Marvel, and Ginsberg, *ibid.*, 1939, **61**, 3161).



(IV.)

The melting point of (diphenyl disulphide)-4 : 4′-(dicarboxyimino ethyl ether) dihydrochloride (268—270°) lies very close to that of the corresponding diamide (278°), and it was found that the action of heat (180°) on the former gave an excellent yield of the latter. By this reaction (diphenyl disulphoxide)-4 : 4′-di(carboxyimino ethyl ether) dihydrochloride afforded quantitatively *di-p-carbamylphenyl disulphoxide*. This decomposition (reaction 6) by heat or storage is mentioned by Pinner (*loc. cit.*; cf. Shriner and Neumann, *Chem. Reviews*, 1944, **35**, 357), and Derby (*loc. cit.*) describes the isolation of benzamide from benzimino ethyl ether hydrochloride.

$$R{\cdot}C(OEt){:}\overset{\oplus}{N}H_2\}\overset{\ominus}{Cl} \longrightarrow R{\cdot}CO{\cdot}NH_2 + EtCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Benzenesulphonates of imino-ethers appear not to have been described. Although *benzimino ethyl ether benzenesulphonate* was obtained in excellent yield as a crystalline solid, application of the same method to (IV) gave an uncrystallisable oil.

Ammonolysis of *N*-arylamidines to give the unsubstituted amidines according to equation (7) has been described by Pinner (*loc. cit.*; cf. Shriner and Neumann, *loc. cit.*) and by Oxley and Short (this vol., p. 449) and, since it occurs at a temperature lower than that required for the formation of an unsubstituted amidine from the corresponding cyanide, the possibility of obtaining (I) by this route, through the corresponding di-*N*-phenylamidino-compound was examined. Di-*p*-cyanophenyl disulphoxide and aniline benzenesulphonate (2 mols.) at 180° afforded a quantitative yield of a magnificent dark blue solid, which gave analytical figures for *di*-(p-N-*phenylamidinophenyl*) *disulphoxide dibenzenesulphonate* and showed solubilities in agreement with this structure. The material, softening at 100°, gave a blue solution in alcohol or acetone, from which it was reprecipitated unchanged by ether. Attempted preparation of the base by aqueous or alcoholic alkali was unsuccessful even after long refluxing. Ammonolysis of the blue material by gaseous ammonia, without a solvent or in ethylene glycol, at 180° for 6 hours gave only unchanged material.

$$R{\cdot}C(\overset{\oplus}{N}H_2){\cdot}NHR' + NH_3 \rightleftharpoons R{\cdot}C(\overset{\oplus}{N}H_2){\cdot}NH_2 + NH_2R' \quad . \quad . \quad . \quad . \quad (7)$$

That the blue compound was not the corresponding disulphide derivative was shown by synthesis of the latter. Reaction of di-*p*-cyanophenyl disulphide and aniline benzenesulphonate at 220° gave *di*-(p-N-*phenylamidinophenyl*) *disulphide dibenzenesulphonate* as a white crystalline solid, m. p. 108°. Halssig (*loc. cit.*) reports that at 160—200° aniline toluene-*p*-sulphinate afforded a magnificent dark blue material which was physically and chemically similar to the blue product described above. Moreover, Halssig states that action of heat on the *p*-toluidine and *o*-toluidine salts of the same acid gave, respectively, a reddish-violet and a bluish-violet dye of very similar nature.

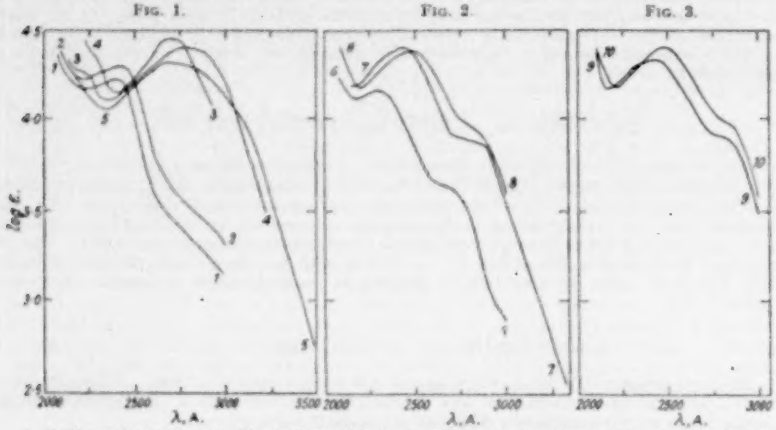
Heating a mixture of di-*p*-cyanophenyl disulphoxide and aniline did not give the blue dye, which was however obtained immediately by the addition of aniline benzenesulphonate to the melt. A mixture of diphenyl disulphoxide and aniline benzenesulphonate, when heated, also gave a deep-blue dye, and it was then found that a blue dye could also be produced from aniline benzenesulphonate alone by heating this to a higher temperature (250—300°) for a longer time. The nature of the blue dye was not further investigated.

In view of the ready conversion of disulphoxides into the corresponding disulphides and the resulting dependence on accurate analytical data, the ultra-violet absorption spectra of the

compounds described above were determined (in alcohol) in order to investigate whether a generalisation capable of distinguishing between the two structures could be discovered.

Aromatic disulphides (p-R·C_6H_4·S)$_2$ (Table) have $\lambda_{max.}$ at 2410 A. when R = H or Me (cf. also Fox and Pope, *J.*, **1913**, **1263**; Lyons, *Nature*, **1948**, **162**, 1004; Koch, this vol., p. 394), and the introduction of an unsaturated bond into the group R causes a bathochromic and hyperchromic displacement of +300—400 A. (Fig. 1).

FIG. 1. FIG. 2. FIG. 3.



1. *Diphenyl disulphide.*—2. *Di-p-tolyl disulphide.*—3. *Di-p-cyanophenyl disulphide.*—4. *Di-p-amidinophenyl disulphide dibenzenesulphonate.*—5. *(Diphenyl disulphide)-4 : 4'-di(carboxyimino ethyl ether) dihydrochloride.*—6. *Diphenyl disulphoxide.*—7. *Di-p-cyanophenyl disulphoxide.*—8. *(Diphenyl disulphoxide)-4 : 4'-di(carboxyimino ethyl ether) hydrochloride.*—9. *Di-p-carbamylphenyl disulphoxide.*—10. *Diphenyl disulphoxide di(imino ethyl ether).*

The corresponding disulphoxides p-R·C_6H_4·SO_2·S·C_6H_4·R-p (Table), in which one sulphur atom is devoid of unshared electrons, have $\lambda_{max.}$ at 2300 A. when R = H, while the bathochromic and hyperchromic displacement caused by the introduction of an unsaturated centre into the group R of the disulphoxides is much smaller (+150 to 200 A.) than it is for the corresponding disulphides. The disulphoxides examined show a characteristic marked inflexion at 2720—2900 A. (Figs. 2 and 3).

Absorption spectra of disulphides, (p-R·C_6H_4·S)$_2$, *and disulphoxides,* p-R·C_6H_4·SO_2·S·C_6H_4·R-p.

	Disulphide.		Disulphoxide.	
R =	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$
H	2410	4·22	2300—2310	4·15
			2720 •	3·60
Me	2420	4·29	—	—
NH_2,HCl	2540—2560	4·21	—	—
	2900	3·91		
CN	2670—2730	4·41	2430—2440	4·40
			2910 •	3·85
$C\langle^{OEt}_{NH}$	—	—	2490—2500	4·40
			2830 •	3·99
$C\langle^{OEt}_{NH_2Cl}$	2710—2750	4·31	2460—2480	4·39
			2830 •	3·96
$C\langle^{NH_2}_{NH_2Cl}$	2800—2840	4·38	—	—
$C\langle^{NH_2}_{NH_2X}$ †	2800—2850	4·39	—	—
CO·NH_2	—	—	2400—2440	4·34
			2830 •	3·88

• Inflexion. † X = C_6H_4·SO_2.

Examination of the ultra-violet absorption spectra thus not only affords valuable confirmatory evidence of the structure of (IV) but also makes it possible to distinguish readily between aromatic disulphides and disulphoxides.

Experimental.

Di-p-cyanophenyl Disulphoxide.—A solution of sodium *p*-cyanobenzenesulphinate (18·9 g., 0·1 mol.) in water (135 c.c.) was cooled to 0° and acidified strongly with concentrated hydrochloric acid (250 c.c.). The solution was set aside at 0° for 2 days, saturated with salt, and extracted with chloroform. Removal of solvent from the washed and dried (Na_2SO_4) chloroform extracts and crystallisation of the residue from alcohol gave white needles (7 g., 70%) of di-*p*-cyanophenyl disulphoxide, m. p. 158—159° (Cymerman, Koebner, and Short, *loc. cit.*, give m. p. 158—159°).

The original aqueous mother-liquors after extraction with chloroform were evaporated to half-bulk *in vacuo* and filtered, and the filtrate was treated with a solution of *p*-toluidine (7 g.) in hot dilute hydrochloric acid (5*N*.; 100 c.c.). Cooling to 0° gave white plates (4 g., 45%) of *p-toluidine* p-*cyanobenzenesulphonate* (Found : N, 9·55. $C_{14}H_{14}O_3N_2S$ requires N, 9·65%), m. p. 241°, undepressed on admixture with an authentic specimen (m. p. 241°) prepared from *p*-cyanobenzenesulphonyl chloride.

Di-p-amidinophenyl Disulphide.—Method A. (*a*) A mixture of di-*p*-cyanophenyl disulphoxide (4·5 g.) and ammonium thiocyanate (11 g., 10 mols.) was heated at 180° (bath temperature) for 3 hours with stirring. The cooled melt was then extracted with boiling water (300 c.c.) and filtered, and the filtrate basified at 0° (ice) with sodium hydroxide solution (10*N*.). The precipitated diamidine was collected on a funnel, washed with ice-water, and dissolved in the minimum amount of boiling hydrochloric acid (5*N*.). Cooling afforded white needles of *di-p-amidinophenyl disulphide dihydrochloride hemihydrate* (3·5 g., 82·5%), m. p. 316° (Found : N, 14·6; H_2O, 2·1. $C_{14}H_{14}N_4Cl_2S_2,\frac{1}{2}H_2O$ requires N, 14·6; H_2O, 2·35%). Drying at 120° gave the anhydrous *salt* (Found : C, 45·1; H, 4·35; N, 14·8, 14·75. $C_{14}H_{14}N_4Cl_2S_2$ requires C, 44·8; H, 4·3; N, 14·9%), m. p. 310—311°.

(*b*) The base precipitated from a fusion identical with that of (*a*) was dissolved in the minimum of hot aqueous benzenesulphonic acid. On cooling, *di-p-amidinophenyl disulphide dibenzenesulphonate* separated (6·75 g., 97%) as white needles, m. p. 253—254° (Found : C, 50·3; H, 4·2; N, 8·95. $C_{26}H_{26}O_6N_4S_4$ requires C, 50·5; H, 4·2; N, 9·05%).

(*c*) Equivalent quantities of the diamidine dihydrochloride and sodium picrate in the minimum of hot water were mixed and the quantitatively-formed yellow precipitate was recrystallised from aqueous 2-ethoxyethanol, giving the *dipicrate* as yellow needles, m. p. 257° (decomp). (Found : N, 18·35. $C_{26}H_{20}O_{14}N_{10}S_2$ requires N, 18·4%).

(*d*) Addition of excess of sodium benzoate solution to a solution of the diamidine dihydrochloride and recrystallisation of the white precipitate from methanol–ether afforded white crystals of the *dibenzoate dihydrate*, m. p. 250° (decomp.) (Found : C, 58·05, 58·1; H, 4·85, 5·05; N, 9·65, 9·5. $C_{28}H_{26}O_4N_4S_2,2H_2O$ requires C, 57·75; H, 5·15; N, 9·6%).

Method B. (*a*) A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and ammonium benzenesulphonate (7 g., 2 mols.) was stirred at 180° (bath) in an atmosphere of ammonia for 7 hours, the mixture becoming mobile after 2—3 hours. It was extracted with boiling water (400 c.c.), the filtrate basified at 0° (ice) with sodium hydroxide solution (10*N*.) and the base washed with ice-water on the filter. Dissolved in the minimum of hot dilute hydrochloric acid (5*N*.), it gave on cooling white needles of di-*p*-amidinophenyl disulphide dihydrochloride (2·3 g., 51%), m. p. 310—311° (decomp.), undepressed on admixture with the substance (m. p. 310—311°) from method *A* (Found : C, 44·8, 44·5, 45·1; H, 4·2, 4·05, 4·5; N, 14·35, 14·35%).

(*b*) An identical fusion, followed by dissolution of the base obtained in benzenesulphonic acid afforded the dibenzenesulphonate, m. p. 253—255° (4·8 g., 65%), as white needles (Found : C, 49·7; H, 4·7; N, 8·65%). It did not depress the m. p. of a sample (m. p. 253—254°) from method *A*.

(*c*) The dipicrate was obtained as very small yellow crystals (from 2-ethoxyethanol), m. p. 259° (decomp.) (Found : N, 17·75%), undepressed on admixture with the substance (m. p. 257°) from method *A*.

(*d*) The dibenzoate dihydrate was obtained as white crystals, m. p. 249° (decomp.) (Found : C, 58·1; H, 4·75; N, 9·33%). A mixed m. p. with the material (m. p. 250°) from method *A* was undepressed.

Method C. A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and ammonium benzenesulphonate (14 g., 4 mols.) was heated at 250—255° for 2 hours. The reaction mixture was extracted with boiling water, and the filtrate on cooling deposited white needles (6 g., 81%) of the dibenzenesulphonate, m. p. 250—254° (Found : C, 50·15; H, 4·4; N, 8·95%), undepressed on admixture with a sample (m. p. 253—254°) from method *A*. The aqueous mother-liquors on evaporation to dryness *in vacuo* left a solid residue (12 g.) from which ammonium benzenesulphonate was removed by extraction with cold water, leaving a white solid (2 g., 62·5%) crystallising from hot water in needles, m. p. >360°, of benzamidine-*p*-sulphonic acid (Found : N, 13·85. Calc. for $C_7H_8O_3N_2S$: N, 14·0%). Remsen and Muckenfuss (*Amer. Chem. J.*, 1896, **18**, 353) give m. p. >360°.

Method D. A solution of di-*p*-cyanophenyl disulphide (0·9 g.) in dry chloroform (20 c.c.) and dry alcohol (10 c.c.) was saturated with hydrogen chloride at 0° and set aside at room temperature for 8 days. Addition of dry ether gave (*diphenyl disulphide*)-4 : 4'-*di*(*carboxyimino ethyl ether*) *dihydrochloride* (1·4 g., 96%) as a white microcrystalline solid, m. p. (sealed tube) 268—270° (decomp.) after foaming at 120° (Found : N, 6·8. $C_{18}H_{20}O_4N_4Cl_2S_2$ requires N, 6·5%).

The dihydrochloride (1 g.) was suspended in dry alcohol (20 c.c.) saturated with ammonia at 0°, and set aside for 10 days. The alcoholic solution was poured into dry ether, the precipitate dissolved in dilute hydrochloric acid, and converted, *via* the base, into the diamidine dibenzenesulphonate (0·75 g., 53%), m. p. 253—255° (Found : N, 8·95%), which did not depress the m. p. of a sample (m. p. 253—254°) prepared by method *A*. This was converted, *via* the base, into the dihydrochloride, m. p. 310—311°

(Ashley, Barber, Ewins, Newbery, and Self, *loc. cit.*, give m. p. >300°), which did not depress the m. p. of the material (m. p. 310—311°) obtained by method *A*.

Method E. A mixture of di-*p*-cyanophenyl disulphide (2 g.) and ammonium thiocyanate (6 g.) was heated at 180° (bath) for 3 hours with stirring. Working-up as described above (method *A*) afforded white needles (1·6 g., 35%) of the dibenzenesulphonate, m. p. 253—255°, undepressed on admixture with a sample (m. p. 253—254°) prepared by method *A* (Found: N, 8·6, 8·5%).

The picrate crystallised from acetone–light petroleum (b. p. 40—60°) in yellow needles, m. p. 253° (decomp.) (Found: N, 18·1%), which showed no depression when mixed with the substance (m. p. 257°) from method *A*.

Method F. (*a*) A solution of di-*p*-cyanophenyl disulphoxide (6 g.) in chloroform (70 c.c.) and absolute alcohol (40 c.c.) was treated with dry hydrogen chloride at 0°, set aside at room temperature for 5 days, and then shaken for 6 hours. Addition of dry ether afforded *(diphenyl disulphoxide)* **4** : **4**′-*di(imino diethyl ether) dihydrochloride* (9·2 g., 100%) as a white solid, m. p. (sealed tube) 225—230° (decomp.) after foaming at 120°, and forming a meniscus at 275—280° (Found: C, 45·9; H, 4·9; N, 6·25. $C_{18}H_{22}O_4N_2Cl_2S_2$ requires C, 46·5; H, 4·7; N, 6·0%).

(*b*) A mixture of this dihydrochloride (0·5 g.), anhydrous potassium carbonate (0·5 g.), and chloroform (50 c.c.) was shaken with water (25 c.c.), and the chloroform layer separated. The aqueous phase was extracted with chloroform, and the combined extracts dried (Na_2SO_4). Removal of solvent to small bulk and addition of light petroleum (b. p. 40—60°) afforded white cubes of *(diphenyl disulphoxide)*-**4** : **4**′-*di(carboxyimino ethyl ether) hemihydrate*, m. p. 220° (decomp.) (Found: C, 53·9; H, 5·6; N, 6·75, 6·55. $C_{18}H_{20}O_4N_2S_2,\frac{1}{2}H_2O$ requires C, 53·9; H, 5·3; N, 7·0%).

(*c*) A solution of the dihydrochloride obtained in (*a*) above (4·5 g.) in absolute alcohol (50 c.c.) saturated with ammonia at 0° was allowed to stand for 6 days. Addition of ether gave the crude diamidine dihydrochloride (4·0 g., 100%) which after purification *via* the base had m. p. 310—311°, undepressed on admixture with the compound (m. p. 310—311°) from method *A*. This was converted into the dibenzenesulphonate, m. p. 253—254° (Found: C, 50·1; H, 4·6; N, 8·95%) which showed no depression with the compound (m. p. 253—254°) from method *A*.

Di-p-carbamylphenyl Disulphide.—A small quantity of diphenyl disulphide **4** : **4**′-di-imino diethyl ether dihydrochloride was heated at 180° (bath) for 1 hour. The residue, crystallised from acetic acid, gave white needles of di-*p*-carbamylphenyl disulphide, m. p. 276—277°. A mixed m. p. with an authentic specimen (McClelland and Warren, *J.*, 1930, 1102; m. p. 278°) gave no depression.

Di-p-carbamylphenyl Disulphoxide.—Heated at 180° (bath) for 1 hour, the disulphoxide di-iminoether dihydrochloride (0·5 g.) afforded 0·48 g. (100%) of *di-p-carbamylphenyl disulphoxide* as a white microcrystalline solid, m. p. 225—230° (decomp.), forming a meniscus at 275—280° (Found: N, 8·35. $C_{14}H_{12}O_4N_2S_2$ requires N, 8·35%).

Action of Ammonia on Di-p-cyanophenyl Disulphoxide.—A solution of di-*p*-cyanophenyl disulphoxide (0·5 g.) in ethylene glycol (10 c.c.) was kept at 180° for 2 hours in an atmosphere of ammonia. The solution was cooled, poured into water, and extracted with chloroform. Removal of solvent from the dried chloroform extracts afforded a residue (0·15 g.) which when purified by sublimation (0·01 mm.) and crystallisation from chloroform–light petroleum (b. p. 40—60°) had m. p. 165—168°, undepressed on admixture with di-*p*-cyanophenyl disulphide (m. p. 172—173°). A mixture with the starting material (m. p. 157—158°) gave a 30° depression in m. p.

Di-(p-N-phenylamidinophenyl) Disulphoxide Dibenzenesulphonate.—A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and aniline benzenesulphonate (10 g., 2 mols.) was heated at 180° (bath) for 2 hours, the mixture becoming mobile after 0·5 hour and then viscous after 1·4 hours. The cooled reaction mixture, recrystallised from alcohol–ether, gave a deep-blue *salt* (16 g., 100%), softening at 100° (Found: N, 7·0. $C_{38}H_{34}O_6N_6S_4$ requires N, 7·0%). It was soluble in methanol or acetone, moderately soluble in alcohol, sparingly soluble in isopropanol or water, and insoluble in ether.

Di-(p-N-phenylamidinophenyl) Disulphide Dibenzenesulphonate.—A mixture of di-*p*-cyanophenyl disulphide (0·1 g.) and aniline benzenesulphonate (0·38 g.) was heated at 220° (bath) for 2 hours. Extraction with boiling water afforded, on cooling, white prisms of the *dibenzenesulphonate*, m. p. 108° (Found: N, 6·85, 6·85. $C_{38}H_{34}O_6N_6S_4$ requires N, 7·25%).

Benzimino Ethyl Ether Benzenesulphonate.—Equivalent quantities of the benzimino-ether hydrochloride and potassium carbonate in the minimum amount of water were mixed and the free base was at once extracted with ether. The dried (Na_2SO_4) ethereal solution was added to a solution of benzenesulphonic acid in methanol. Cooling gave colourless needles, m. p. 137°, of *benzimino ethyl ether benzenesulphonate* (Found: N, 4·6. $C_{14}H_{15}O_4NS$ requires N, 4·55%).

This work was carried out under the auspices of the National Health and Medical Research Council, to whom thanks are due for financial assistance. The authors also thank Miss J. Fildes for microanalyses and Dr. W. F. Short for kindly affording facilities for a number of microanalyses.

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24. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part I. The Synthesis of a Geometrical Isomer of Herculin.*

By R. A. Raphael and Franz Sondheimer.*

Attempts to synthesise the insecticide herculin (I; configuration about the double bonds unknown) are described. The diacetylenic analogue (VI) and the *cis*-ethylenic-acetylenic analogue (XV) have been prepared by the methods indicated in the scheme on p. 116. Partial hydrogenation of these compounds gave the isobutylamide of undeca-1(*cis*) : 7(*cis*)-diene-1-carboxylic acid (*cis-cis* herculin) (I); this was not identical with the natural insecticide.

A pungent *N*-*iso*butyl unsaturated acid amide has been isolated from the bark of the southern prickly ash, *Zanthoxylum clavaherculis* L., by Jacobson (*J. Amer. Chem. Soc.*, 1948, **70**, 4234). The substance, which was shown to have the structure (I) (*N*-*iso*butylundeca-1 : 7-diene-1-carboxyamide), has approximately the same order of paralysing action and toxicity to house flies as the pyrethrins, and is also toxic to several other species of insects. When the synthesis of a compound of this structure is considered, it becomes apparent that any one of four configurations is possible according to the geometrical isomerism about the double bonds (*trans-trans*, *trans-cis*, *cis-trans*, and *cis-cis*). No speculation about the configuration of the natural compound was made by Jacobson.

We have synthesised by two routes a compound of structure (I), possessing the *cis*-configuration about both double bonds; this, however, was not identical with natural herculin, and the latter must therefore have one of the three remaining configurations.

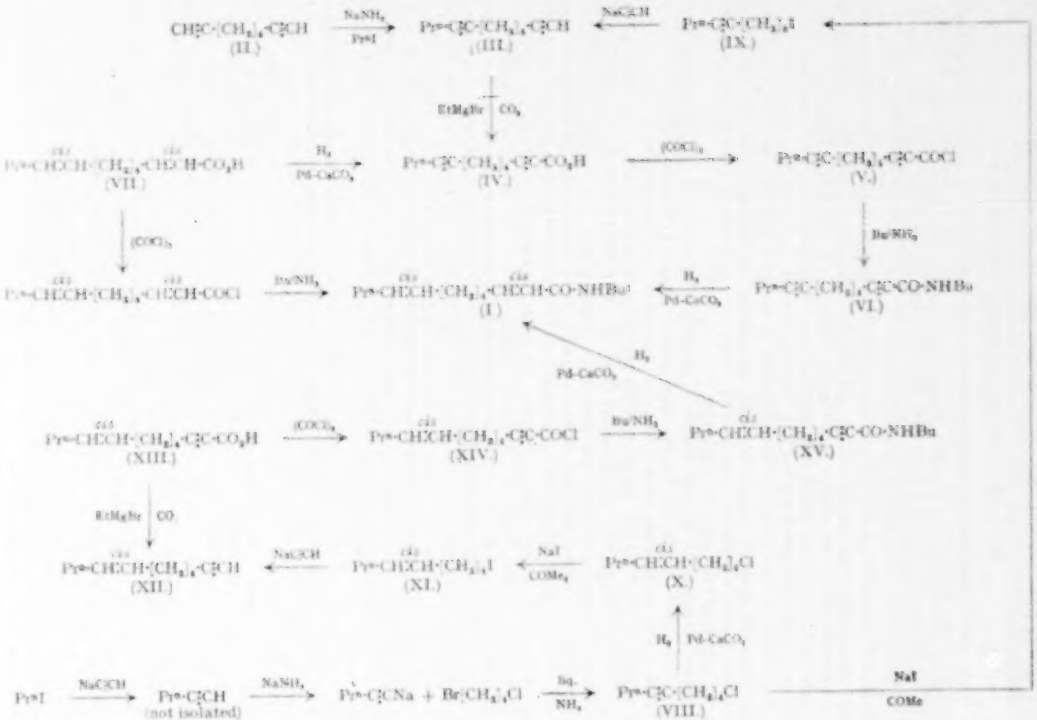
When octa-1 : 7-diyne (II) (prepared from tetramethylene dibromide and sodium acetylide as described by Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619) was treated first with 1·1 moles of sodamide in liquid ammonia, and then with propyl iodide, the required monoalkylation product *undeca*-1 : 7-*diyne* (III) was obtained in 80% yield (allowing for the recovered starting material). This type of differential condensation of a diacetylene has been found to be of general applicability, and it has been employed in other syntheses (Sondheimer, forthcoming publication; Leese and Raphael, forthcoming publication). The Grignard complex of (III) was carbonated with solid carbon dioxide at atmospheric pressure to give *undeca*-1 : 7-*diyne*-1-*carboxylic acid* (IV) (*S-benzylthiuronium* salt) in 65% yield, the structure of which was confirmed by hydrogenation to lauric acid. Heating (IV) under reflux with oxalyl chloride (*cf.* Adams and Ulich, *J. Amer. Chem. Soc.*, 1920, **42**, 599) produced the acid chloride (V) which on treatment with excess of *iso*butylamine furnished the crystalline diacetylenic *N*-*isobutyl-amide* (VI) in excellent yield. When this absorbed two moles of hydrogen in the presence of a palladium–calcium carbonate catalyst, *N*-*isobutylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*herculin*) (I) was obtained as a homogeneous liquid.

The formulation of this compound, and others described below, as the *cis-cis*-isomer, is based on many recorded observations regarding the catalytic hydrogenation of triple bonds (*inter al.*, Bourguel, *Bull. Soc. chim.*, 1929, **45**, [4], 1067; Stoll and Rouvé, *Helv. Chim. Acta*, 1938, **21**, 1542; *idem*, *Ber.*, 1940, **73**, 1358; Campbell *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 216, 2683; *Chem. Reviews*, 1942, **31**, 90; Lauer and Gensler, *J. Amer. Chem. Soc.*, 1945, **67**, 1171; Ahmad, Bumpus, and Strong, *ibid.*, 1948, **70**, 3391). However, infra-red absorption has indicated that this type of hydrogenation (employing a palladium–calcium carbonate catalyst at room temperature) may also give rise to a small proportion of the *trans*-isomer (Sondheimer, forthcoming publication); for convenience this fact is neglected in the nomenclature of the hydrogenation compounds described in this paper.

Alternatively, the acid (IV) was partially hydrogenated to *undeca*-1(cis) : 7(cis)-*diene*-1-*carboxylic acid* (VII) (*S-benzylthiuronium* salt). The structure of this acid was confirmed by its light-absorption properties, the intensity of absorption at 2160 A. being double that of the unchanged acetylenic acid (IV) (*cf.* Braude, *Ann. Reports*, 1945, **42**, 105; Haynes and Jones, *J.*, 1946, 503). Heating this acid under reflux with oxalyl chloride gave the corresponding acid chloride, which, undistilled, reacted with *iso*butylamine to product an excellent yield of (I), identical with that obtained above.

The second route to *cis-cis*-herculin (I) employs the differential reaction of a mixed dihalide with a sodium acetylide (*cf.* Henne and Greenlee, *J. Amer. Chem. Soc.*, 1945, **67**, 484; Ahmad, Strong, *et al.*, *ibid.*, 1948, **70**, 1099, 3391; Newman and Wotiz, *ibid.*, 1949, **71**, 1292).

* This work was started independently by the two authors; when this was realised, it was decided to publish the results jointly.


Pyr·I
NaC≡CH
Pyr·C≡CH
(not isolated)
NaNH₂
Pyr·C≡CNa + Br[CH₂]₄Cl
liq. NH₃
Pyr·C≡C·[CH₂]₄Cl
(VIII.)
NaI
COMe
H₂ Pd-CaCO₃
Pyr·CH=CH·[CH₂]₄Cl
(X.)
NaI
COMe
Pyr·CH=CH·[CH₂]₄I
(XI.)
NaC≡CH
Pyr·CH=CH·[CH₂]₄·C≡CH
(XII.)
EtMgBr
CO₂
Pyr·CH=CH·[CH₂]₄·C≡C·CO₂H
(XIII.)
(COCl)₂
Pyr·CH=CH·[CH₂]₄·C≡C·COCl
(XIV.)
BuNH₂
Pyr·CH=CH·[CH₂]₄·C≡C·CO·NHBu
(XV.)
H₂
Pd-CaCO₃
Pyr·C≡C·[CH₂]₄C≡C·CO·NHBu
(VI.)
H₂
Pd-CaCO₃
Pyr·CH=CH·[CH₂]₄·CH=CH·CO·NHBu
(I.)
BuNH₂
Pyr·CH=CH·[CH₂]₄·CH=CH·COCl
(VII.)
(COCl)₂
Pyr·CH=CH·[CH₂]₄·CH=CH·CO₂H
(VII.)
H₂
Pd-CaCO₃
Pyr·C≡C·[CH₂]₄C≡C·CO₂H
(IV.)
(COCl)₂
Pyr·C≡C·[CH₂]₄C≡C·COCl
(V.)
BuNH₂
EtMgBr
CO₂
NaNH₂
PyrI
CH≡C·[CH₂]₄·C≡CH
(II.)
Pyr·C≡C·[CH₂]₄·C≡CH
(III.)
NaC≡CH
Pyr·C≡C·[CH₂]₄I
(IX.)

Condensation of propyl iodide with sodium acetylide (this must not be made from sodamide; see Experimental) in liquid ammonia gave pent-1-yne, which, because of its volatility, was not isolated, but converted into its sodium salt by addition of 1 mole of sodamide. Reaction with 1-chloro-4-bromobutane (prepared from tetrahydrofuran as described by Newman and Wotiz, *loc. cit.*) gave *1-chlorodec-5-yne* (VIII) in 64% yield. Refluxing the chloro-compound with sodium iodide in acetone gave the iodo-compound (IX) which was condensed without purification with sodium acetylide in liquid ammonia. The undeca-1 : 7-diyne (III) thus obtained in 44% yield had identical physical properties with that obtained above.

Partial hydrogenation of the acetylenic chloride (VIII) in the presence of a palladium–calcium carbonate catalyst, or better Raney nickel, gave *1-chlorodec-5(cis)-ene* (X), which when heated under reflux with sodium iodide in acetone yielded the iodide (XI). The crude iodide was condensed with sodium acetylide in liquid ammonia whereby *undec-7(cis)-en-1-yne* (XII) was obtained in 62% yield (based on (X)). Carbonation of the Grignard complex of (XII) at atmospheric pressure gave *undec-7(cis)-en-1-yne-1-carboxylic acid* (XIII) in 57% yield. The acid chloride (XIV), prepared by refluxing the acid with oxalyl chloride, was condensed with excess of *iso*butylamine and *N-isobutylundec-7(cis)-en-1-yne-1-carboxyamide* (XV) was formed. Partial hydrogenation in the presence of a palladium–calcium carbonate catalyst then gave *cis-cis*-herculin (I), having physical properties identical with those of (I), prepared as above.

The *cis-cis*-analogue (I), obtained by these routes, was a colourless liquid, which could not be induced to crystallise, whereas natural herculin is a crystalline solid, m. p. 59—60°. Moreover it was quite stable at room temperature, whereas natural herculin (Jacobson, *loc. cit.*) has been reported to be unstable under these conditions. Again it shows none of the physiological properties (burning taste, etc.) described by the American author.

The structure of (I) was rigidly confirmed by complete hydrogenation to the crystalline *N-iso*butyl-lauramide, and by potassium permanganate oxidation, whereby the three fragments (butyric, adipic, and *N-iso*butyloxamic acids) were isolated in yields very similar to those obtained by Jacobson (*loc. cit.*) for the natural herculin.

The three herculin analogues, *cis-cis*-herculin (I), 1 : 2-dehydro-*cis*-herculin (XV), and 1 : 2 : 7 : 8-tetradehydroherculin (VI), are being tested by Dr. R. A. E. Galley of the Agricultural Research Council for insecticidal properties, and the results will be recorded later.

Attempts to convert both the *cis-cis*-acid (VII) and the *cis-cis-N-iso*butyl-amide (I) into the *trans-trans*-compounds by various methods have so far been unsuccessful. Thus even when the acid (VII) was heated with selenium at 200° for 10 minutes (cf. Ahmad, Bumpus, and Strong, *J. Amer. Chem. Soc.*, 1948, **70**, 3391), it was recovered unchanged. It is known however that the partial reduction of an acetylene with sodium in liquid ammonia leads to the *trans*-ethylenic compound (Campbell and Eby, *J. Amer. Chem. Soc.*, 1941, **63**, 216, 2683; Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 90; Sondheimer, forthcoming publication). Application of this method to the analogues (VI) and (XV) should furnish the 1(*trans*) : 7(*trans*)- and 1(*trans*) : 7(*cis*)-herculins. It is now considered that the latter isomer will most probably be identical with the natural compound (cf. the short discussion presented in the following paper regarding the stereochemical configuration of the closely related insecticide, pellitorine), and further work on these compounds is now in progress in these laboratories. Moreover the methods described in this paper are being used for the synthesis of the various possible stereoisomers of other related insecticides, and the preparation of a geometrical isomer of the insecticide pellitorine is described in the following communication.

Experimental.

(Light-absorption data were determined in ethanol.)

Undeca-1 : 7-diyne (III).—To a suspension of sodamide in liquid ammonia (150 c.c.) [from sodium (5·0 g.), the ferric nitrate catalyst described by Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) being used to catalyse the transformation] octa-1 : 7-diyne (21·2 g.) in dry ether (25 c.c.) was added during 10 minutes with stirring and cooling (alcohol–carbon dioxide). The reaction mixture was stirred for 2 hours, and propyl iodide (41 g.) in ether (30 c.c.) was gradually added. Stirring was continued for another 6 hours, the temperature being kept at *ca.* −40°. The solvent was evaporated on the steam-bath, water and ether were added, and the ether layer after being washed with water, dilute sulphuric acid, and sodium hydrogen carbonate solution, was dried and evaporated. Distillation of the residue through a short Vigreux column gave unchanged octadiyne (9·2 g.) and *undeca-1 : 7-diyne* (14·4 g., 86% yield, 49% conversion) as a mobile pleasant-smelling liquid, b. p. 97—99°/20 mm., n_D^{20} 1·4576 (Found: C, 89·75; H, 10·9. $C_{11}H_{16}$ requires C, 89·1; H, 10·9%). In addition, a product (2·1 g.) was obtained, b. p. 135—140°/18 mm., n_D^{20} 1·4650, believed to be the dialkylation product, tetradeca-4 : 10-diyne; this was not further investigated.

When propyl bromide was substituted for the iodide in the above experiment, the yield of undecadiyne was considerably reduced.

Undeca-1 : 7-*diyne*-1-*carboxylic Acid* (IV).—Undeca-1 : 7-diyne (7·4 g.) in dry ether (20 c.c.) was added during 5 minutes to a stirred solution of ethylmagnesium bromide (from magnesium, 1·6 g.) in ether (120 c.c.) in an atmosphere of nitrogen. The solution was heated under reflux for 90 minutes, and then cooled in ice. It was poured on to a large excess of solid carbon dioxide in a conical flask, and the flask was shaken occasionally. After *ca.* 1 hour, when most of the solid had disappeared, more solid carbon dioxide was added, and the mixture was set aside overnight. The solid complex was decomposed with dilute sulphuric acid, and the ethereal layer was washed with water and sodium hydrogen carbonate solution. The latter extract was washed with ether, acidified, and again shaken with ether. This last ether extract was dried, evaporated, and the residue distilled. *Undeca*-1 : 7-*diyne*-1-*carboxylic acid* (8·2 g., 65%) was obtained as a colourless liquid, b. p. 134—135°/10^{-2} mm., n_D^{25} 1·4882 (Found : C, 75·3; H, 8·55. $C_{11}H_{14}O_2$ requires C, 75·0; H, 8·4%). Light absorption : $\varepsilon = 6{,}700$ (λ, 2160 A.). The *S-benzylthiuronium* salt crystallised from a large volume of ethyl acetate in plates, m. p. 174° (Found : C, 67·25; H, 7·45; N, 7·95. $C_{20}H_{24}O_2N_2S$ requires C, 67·0; H, 7·3; N, 7·8%).

The acid (0·55 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption was complete (274 c.c. of gas were absorbed at 16°/760 mm., equivalent to 4·05 ⁻). The residue (0·56 g.), after removal of the catalyst and solvent, completely solidified, and then had m. p. 43° undepressed on admixture with an authentic sample of lauric acid.

Undeca-1 : 7-*diyne*-1-*carboxyl Chloride*. (V).—The diacetylenic acid (3·0 g.) and oxalyl chloride (7·5 g.) were heated under reflux for 40 minutes (gas evolution ceased after *ca.* 25 minutes). The excess of oxalyl chloride was removed at the water-pump, the temperature being kept below 60°. The residue was rapidly distilled to give the acid chloride (2·6 g.) as a mobile pungent liquid, b. p. 97—99°/10^{-2} mm., n_D^{25} 1·4903, which hydrolysed too rapidly in air to permit of accurate analysis.

In another experiment, in which the excess of oxalyl chloride was removed at too high a temperature, considerable polymerisation occurred, and only a very poor yield of the required acid chloride was obtained.

N-iso*Butylundeca*-1 : 7-*diyne*-1-*carboxyamide* (VI).—A solution of *iso*butylamine (4·5 g.) in dry ether (10 c.c.) was added dropwise during 5 minutes to the diacetylenic acid chloride (V) (2·6 g.) in ether (10 c.c.), with ice cooling and continuous shaking. After 1 hour at room temperature, the reaction mixture was diluted with more ether and washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried extract was evaporated to give the diacetylenic N-iso*butyl-amide* (2·95 g.) as a colourless liquid, which completely solidified on cooling and then had m. p. 45—47°. One crystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 47—48°, not raised by further crystallisation (Found : C, 77·35; H, 10·35; N, 5·65. $C_{15}H_{21}ON$ requires C, 77·7; H, 10·2; N, 5·65%).

N-iso*Butylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*Herculin*) (I) *from* (VI).—The diacetylenic N-*iso*butyl-amide (VI) (1·14 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·14 g.; 2% Pd) until 2 moles of hydrogen (222 c.c. at 18°/768 mm.) had been absorbed. The residue, after removal of the catalyst and solvent, was distilled to give cis-cis-*herculin* (0·91 g.) as a colourless liquid, b. p. 140—142°/10^{-2} mm., n_D^{25} 1·4838 (Found : C, 76·25; H, 11·7; N, 5·65. $C_{15}H_{25}ON$ requires C, 76·45; H, 11·65; N, 5·55%).

Undeca-1(cis) : 7(cis)-*diene*-1-*carboxylic Acid* (VII).—The diacetylenic acid (IV) (4·68 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·3 g.; 2% Pd) until 2 moles of hydrogen (1174 c.c. at 19°/771 mm.) had been absorbed (no reaction of the calcium carbonate substrate with the acid was detectable). The catalyst was filtered off, the solvent evaporated, and the residue distilled. This gave the diethylenic *acid* (4·3 g.) as a colourless liquid, b. p. 108—109°/10^{-2} mm., n_D^{25} 1·4740—1·4742 (Found : C, 73·9; H, 10·55. $C_{11}H_{16}O_2$ requires C, 73·45; H, 10·3%). Light absorption : $\varepsilon = 13{,}700$ (λ, 2160 A.). The *S-benzylthiuronium* salt crystallised from ethyl acetate in plates, m. p. 129—130° (Found : N, 7·85. $C_{20}H_{28}O_2N_2S$ requires N, 7·75%).

N-iso*Butylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*Herculin*) (I) *from* (VII).—The diethylenic acid (1·4 g.) (VII) and oxalyl chloride (3·6 g.) were heated under reflux for 1 hour. The excess of oxalyl chloride was removed at the water-pump, and dry benzene was added to the residue, which was again concentrated at the water-pump to give the crude acid chloride (1·65 g.) as a yellow pungent liquid, n_D^{25} 1·4800.

A solution of *iso*butylamine (2·7 g.) in dry ether (10 c.c.) was added dropwise during 5 minutes to the crude acid chloride (1·63 g.) in ether (10 c.c.), with ice-cooling and continuous shaking. After 20 minutes, the product was isolated as described above, and distillation gave *cis-cis*-herculin (1·6 g.), b. p. 145—146°/10^{-2} mm., n_D^{25} 1·4824—1·4827.

1-*Chloronon*-5-*yne* (VIII).—Sodium (5·5 g.), in small pieces, was added to liquid ammonia (300 c.c.) through which acetylene was bubbled, with stirring and cooling (alcohol–carbon dioxide), at such a rate that the blue colour just disappeared before the next piece of sodium was added. The acetylene flow was stopped at the exact moment when the blue colour disappeared after the last piece of sodium had been added (this ensured that no excess of acetylene was present in solution), and propyl iodide (41 g.) was gradually added. The reaction mixture was stirred for 4 hours, and a suspension of sodamide in liquid ammonia (150 c.c.), prepared from sodium (5·8 g.) by aid of the ferric nitrate catalyst, was then added in portions with strong cooling. The mixture was stirred for another 1 hour, and 1-chloro-4-bromobutane (41 g.) was added dropwise. The reaction was completed by stirring and cooling for another 12 hours, and ammonium chloride (15 g.) was added. The ammonia was evaporated off on the steam-bath, water and ether were added to the residue, and the ethereal layer was washed successively with water, dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried extract was evaporated, and distillation of the residue gave unchanged chlorobromobutane (5·3 g.) and 1-*chloronon*-5-*yne* VIII (24·2 g., 64%) as a colourless mobile liquid, b. p. 83—84°/15 mm., n_D^{25} 1·4620 (Found : C, 68·4; H, 9·9. $C_9H_{13}Cl$ requires C, 68·1; H, 9·53%).

In another experiment, propyl bromide (45 g.) was added to a solution of sodium acetylide in liquid ammonia (400 c.c.), prepared by passing acetylene through a suspension of sodamide (from sodium, 8·5 g., with the ferric nitrate catalyst). As the complete conversion of sodamide into sodium acetylide is not accompanied by a well-defined colour change, the presence of excess of dissolved acetylene in the

sodium acetylide solution so formed cannot be avoided. After 3 hours' stirring, a suspension of sodamide in liquid ammonia (200 c.c.), prepared from sodium (9 g.) with the ferric nitrate catalyst, was added in portions. The cooled reaction mixture was stirred for 1 hour, 1-chloro-4-bromobutane (30 g.) was gradually added, and stirring was continued for another 4 hours. After being isolated as described previously, the product was distilled to give 1-chloronon-5-yne (3·0 g., 6%), b. p. 81°/12 mm., n_D^{25} 1·4620. The lower boiling fractions (32 g.) on redistillation gave a colourless liquid, b. p. 37—38°/10 mm., n_D^{25} 1·4461, believed to be 1-chlorohex-5-yne (formed by reaction of the chlorobromobutane with sodium acetylide, produced by the preferential reaction of the second mole of sodamide with the excess of acetylene in solution).

Undeca-1 : 7-*diyne* (III) *from* (VIII).—The chloro-compound (VIII) (2·1 g.) and a solution of sodium iodide (5 g.) in dry acetone (25 c.c.) were heated under reflux for 2 hours. The filtered solution was evaporated, the residue treated with dry ether, and the ethereal solution refiltered. This ether extract, containing the iodide (IX), was added dropwise, with stirring and cooling, to a solution of sodium acetylide in liquid ammonia (500 c.c.), prepared from sodium (3 g.) by the usual catalytic procedure. The reaction mixture was stirred for a further 3 hours, and ammonium chloride (*ca.* 10 g.) was then added. Isolation with ether gave undeca-1 : 7-diyne (0·85 g., 44%), b. p. 95°/15 mm., n_D^{25} 1·4573.

1-*Chloronon*-5(cis)-*ene* (X).—The chloro-compound (VIII) (10·52 g.) in methyl acetate (40 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (1·5 g.; 0·3% Pd), until 1 mole of hydrogen (1582 c.c. at 14°/763 mm.) had been absorbed. The filtered solution was evaporated, and the residue distilled, to give 1-*chloronon*-5-(cis)-*ene* (8·6 g.; 81%) as a colourless mobile liquid, b. p. 75°/12 mm., n_D^{25} 1·4515 (Found: C, 66·9; H, 10·8. $C_9H_{17}Cl$ requires C, 67·25; H, 10·7%). When Raney nickel was substituted for the palladium catalyst, hydrogenation proceeded considerably more rapidly to give a similar yield of (X).

Undec-7(cis)-*en*-1-*yne* (XII).—The chloro-olefin (X) (8·0 g.) was heated under reflux with a solution of sodium iodide (15 g.) in dry acetone (75 c.c.) for 15 hours. The filtered solution was evaporated, and the residue triturated with dry ether, which was again filtered. This ethereal extract, containing the iodide (XI), was added dropwise to a cooled and stirred solution of sodium acetylide (prepared from sodium, 5 g., *via* sodamide by the catalytic method) in liquid ammonia (500 c.c.). The cooled mixture was stirred for another 4 hours, and ammonium chloride (20 g.) was added. The ammonia was evaporated off on the steam-bath, and water and ether were added to the residue. The usual isolation procedure then gave *undec*-7(cis)-*en*-1-*yne* (4·6 g., 62%) as a mobile pleasant-smelling liquid, b. p. 73°/10 mm., n_D^{25} 1·4462 (Found: C, 87·5; H, 12·1. $C_{11}H_{18}$ requires C, 87·9; H, 12·1%).

Undec-7(cis)-*en*-1-*yne*-1-*carboxylic Acid* (XIII).—The hydrocarbon (XII) (4·2 g.) in dry ether (20 c.c.) was added during 5 minutes to a stirred solution of ethylmagnesium bromide (from magnesium, 1·0 g.) in dry ether (50 c.c.) in an atmosphere of nitrogen. The solution was heated under reflux for 2 hours, and the Grignard complex was then carbonated with solid carbon dioxide at atmospheric pressure as already described for the diacetylenic acid. After decomposition with dilute sulphuric acid, the acid fraction was isolated and gave *undec*-7(cis)-*en*-1-*yne*-1-*carboxylic acid* (3·1 g., 57%) as a colourless liquid, b. p. 110°/5 × 10^{-4} mm., n_D^{25} 1·4788—1·4790 (Found: C, 74·4; H, 9·3. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%).

N-iso*Butylundec*-7(cis)-*en*-1-*yne*-1-*carboxyamide* (XV).—The ethylenic acetylenic acid (XIII) (1·5 g.) and oxalyl chloride (3·0 g.) were heated under reflux for 30 minutes. The excess of oxalyl chloride was removed under reduced pressure, dry benzene was added to the residue, and the benzene solution concentrated, to give the crude acid chloride (XIV) as a yellow pungent liquid. This was not distilled, as, in a previous experiment, attempted distillation resulted in extensive polymerisation.

*iso*Butylamine (3·0 g.) in dry ether (10 c.c.) was added dropwise to the acid chloride in dry ether (10 c.c.) with ice-cooling and shaking. After 30 minutes, the product was isolated as described previously, and distillation gave the N-iso*butylundec*-7(cis)-*en*-1-*yne*-1-*carboxyamide* (1·3 g.) as a colourless liquid, b. p. 145—148°/10^{-4} mm., n_D^{25} 1·4876 (Found: C, 77·2; H, 11·0. $C_{16}H_{29}ON$ requires C, 77·65; H, 10·9%).

N-iso*Butylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*Herculin*) (I) *from* (XV).—The *N*-isobutyl-amide (XV) (0·35 g.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·04 g.; 2% of Pd) until 1 mole of hydrogen (35 c.c. at 17·5°/750 mm.) had been absorbed. The filtered solution was evaporated, whereupon distillation gave *cis-cis*-herculin (0·21 g.), b. p. 150—155° (bath temp.)/10^{-4} mm., n_D^{25} 1·4840.

N-iso*Butyl-lauramide*.—*cis-cis*-Herculin (0·21 g.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption was complete (46 c.c. of gas were absorbed at 21°/763 mm., equivalent to 2·2 *H*). Removal of catalyst and solvent, followed by crystallisation of the solid residue from pentane gave *N*-isobutyl-lauramide as needles, m. p. 52—53° (Jacobson, *J. Amer. Chem. Soc.*, 1948, **70**, 4234, gives m. p. 51·5—52°).

Permanganate Oxidation of cis-cis-*Herculin* (I).—This oxidation was carried out with *cis-cis*-herculin (500 mg.) and potassium permanganate (1·7 g.) in water (50 c.c.) in exactly the manner described by Jacobson (*loc. cit.*) for natural herculin. The material not volatile in steam gave *N*-isobutyloxamic acid (230 mg., 82%) as needles, m. p. 105—106° (Jacobson gives 75% yield; m. p. 106—107°), and adipic acid (135 mg., 48%) as prisms, m. p. 150—152° (Jacobson gives 59% yield; m. p. 151—152°). Titration of the steam distillate with 0·1*N*-sodium hydroxide indicated that butyric acid had been obtained in 71% yield. It was identified as its *p*-bromophenacyl ester, m. p. 70°, undepressed on admixture with an authentic specimen (m. p. 70°).

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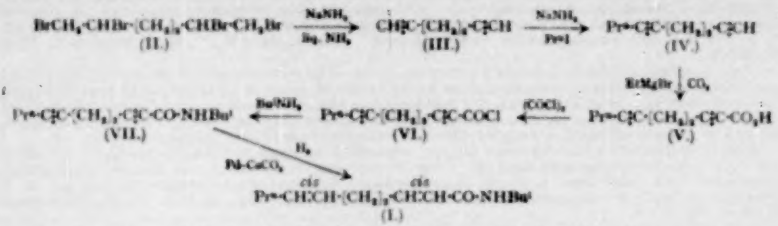
25. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part II. The Synthesis of a Geometrical Isomer of Pellitorine.*

By R. A. Raphael and Franz Sondheimer.

A geometrical isomer of the insecticide pellitorine (I; configuration about the double bonds unknown) has been synthesized by one of the methods used for the preparation of the herculin isomer described in the preceding paper. An improved preparation of dipropargyl (III) is given. The differential monoalkylation of (III), followed by carboxylation, yielded the diacetylenic acid (V), which was converted into the *N-iso*butyl-amide (VII). Partial hydrogenation of this gave *N-iso*butylnona-1(*cis*) : 5(*cis*)-diene-1-carboxyamide (*cis-cis*-pellitorine) (I), which however was not identical with the natural insecticide.

The root of the North African plant *Anacyclus pyrethrum* DC. has been used medicinally to stimulate the activity of the salivary glands and for the alleviation of bronchitis. The powdered root when chewed causes a persistent tingling sensation and partial insensibility of the tongue, accompanied by profuse salivation. The active principle, pellitorine, has been examined by various workers (Bucheim, *Arch. Exp. Path. Pharm.*, 1876, **5**, 455; Dunstan and Garnett, *J.*, 1895, **67**, 100; Schneegans, *Pharm. Ztg.*, 1896, **41**, 668). It was first obtained in the pure state by Gulland and Hopton (*J.*, 1930, 6), who showed it to be an *N-iso*butylnonadienecarboxyamide. The exact location of the double bonds in pellitorine has recently been established by Jacobson (*J. Amer. Chem. Soc.*, 1949, **71**, 366), who showed it to be the *N-iso*butylnona-1 : 5-diene-1-carboxyamide (I; configuration about the double bonds unknown). The American author also found this material (a lower homologue of herculin; cf. preceding paper) to possess insecticidal properties.

The synthesis of the *cis-cis*-isomer (I) has been accomplished by one of the methods employed for the preparation of the herculin isomer described in the previous paper. The starting material, dipropargyl (hexa-1 : 5-diyne) (III), had previously been obtained in rather poor yield (*ca.* 35%) by the dehydrobromination of 1 : 2 : 5 : 6-tetrabromohexane (II) with alcoholic



potassium hydroxide (*inter al.*, Griner, *Ann. Chim.*, 1892, **26**, 347; Lespieau, *ibid.*, 1912, **27**, 152). Heating the tetrabromide with sodamide in light petroleum gave only very small yields of the hydrocarbon (Bourguel, *ibid.*, 1925, **3**, 233). It has been shown that sodamide in liquid ammonia is an efficient and mild dehydrobrominating agent (Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and when the tetrabromide (II) (obtained by the addition of bromine to diallyl) was treated with an excess of this reagent, the diacetylene (III) could be isolated in 56% yield.

When (III) reacted first with 1·1 moles of sodamide in liquid ammonia and then with propyl iodide, the required monoalkylation product, *nona*-1 : 5-*diyne* (IV), was formed in 44% yield. The Grignard complex of (IV) was carbonated with solid carbon dioxide at atmospheric pressure, whereupon the diacetylenic *acid* (V), a crystalline solid, m. p. 87°, was formed. Although the yield obtained in this manner was very poor (*ca.* 8%), it could be increased to 63% by carrying out the reaction under pressure in an autoclave. The acid (V) was converted into the acid chloride (VI) by treatment with oxalyl chloride, excess of *iso*butylamine then giving the crystalline diacetylenic *N-isobutyl-amide* (VII). When this absorbed two moles of hydrogen in the presence of a palladium–calcium carbonate catalyst, the *N-isobutylnona*-1(cis) : 5(cis)-*diene*-1-*carboxyamide* (cis-cis-*pellitorine*) (I) was obtained as a homogeneous liquid. (The reasons for assigning the *cis*-configuration to ethylenic compounds obtained by the catalytic partial hydrogenation of acetylenes has already been given in the previous paper.)

It has been found that the second method used for the synthesis of the herculin isomer could not be applied in this case, as compounds of the type $RC{\equiv}C{\cdot}CH_2{\cdot}CH_2X$ and $R{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2X$ (where X = halogen) on treatment with sodium acetylide in liquid ammonia mainly underwent dehydrohalogenation rather than normal condensation (Sondheimer, forthcoming communication).

The pellitorine isomer (I) obtained by the method described proved to be a somewhat viscous liquid, which could not be induced to crystallise, whereas natural pellitorine is a crystalline solid, m. p. 72° (Gulland and Hopton, *loc. cit.*; Jacobson, *loc. cit.*). Moreover, although (I) had a very bitter taste, it exhibited none of the physiological properties of pellitorine described above.

That (I) differed from pellitorine solely in its geometrical configuration was confirmed by complete hydrogenation to the crystalline *N-iso*butylnonane-1-carboxyamide, and by potassium permanganate oxidation, whereby the three fragments (butyric, succinic, and *N-iso*butyloxamic acid) were isolated in yields very similar to those obtained by Jacobson (*loc. cit.*) for the natural pellitorine.

It is interesting to note the close structural similarity between the acid moiety (VIII) of pellitorine and the violet perfume, nona-2 : 6-dien-1-al (IX). Two methods for the synthesis of the latter have been developed (Ruzicka and Schinz, *Helv. Chim. Acta*, 1934, **17**, 1602; Hunsdiecker, *Chem. Ber.*, 1947, **80**, 137), and application of either of these methods should give

(VIII.) $Pr{\cdot}CH{:}CH{\cdot}[CH_2]_3{\cdot}CH{:}CH{\cdot}CO_2H$ $\qquad$ $Et{\cdot}CH{:}CH{\cdot}[CH_2]_3{\cdot}CH{:}CH{\cdot}CHO$ (IX.)

the acid (VIII) in both the 1(*trans*) : 5(*trans*)- and the 1(*trans*) : 5(*cis*)-configurations. By analogy with the natural nonadienal (IX) and nonadienol (Takei *et al.*, *Bull. Agric. Chem. Soc. Japan*, 1938, **14**, 64; *Chem. Zentr.*, 1938, II, 3096; Ruzicka, Schinz, and Susz, *Helv. Chim. Acta*, 1944, **27**, 1561; Sondheimer, forthcoming publication), and with other αβ-unsaturated acids (cf. English, Bonner, and Haagen-Smit, *J. Amer. Chem. Soc.*, 1939, **61**, 3434; Lauer and Gensler, *ibid.*, 1945, **67**, 1171) the latter configuration is most probably the one present in natural pellitorine. The synthesis of this 1(*trans*) : 5(*cis*)-pellitorine by the methods indicated is now in progress in these laboratories.

Experimental.

Dipropargyl (*Hexa*-1 : 5-*diyne*) (III).—1 : 2 : 5 : 6-Tetrabromohexane was prepared in 95% yield by the gradual addition of the theoretical amount of bromine to a well-cooled solution of diallyl (hexa-1 : 5-diene) in ether, followed by removal of solvent under reduced pressure.

A suspension of sodamide in liquid ammonia (4 l.) was prepared from sodium (322 g., 14 moles), the ferric nitrate catalyst described by Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) being used to catalyse the transformation. Tetrabromohexane (704 g., 1·75 moles) in dry ether (1·6 l.) was added dropwise during 2 hours to the cooled (alcohol–carbon dioxide) and stirred suspension, which was then stirred for another 3 hours. The reaction mixture was set aside overnight without cooling, whereby most of the ammonia evaporated. (It was found advisable to allow the ammonia to evaporate before decomposing the sodio-complex, in order to minimise losses of the volatile product.) Ether, ice, and water were added to the residue, the aqueous layer was washed with ether, and the combined organic extracts were washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and then dried. The solvent (*ca.* 2·5 l.) was removed through a Dufton column; distillation of the residue through the same column gave dipropargyl (76·9 g., 56%) as a colourless liquid, b. p. 87·5—88·5°/758 mm., n_D^{20} 1·4380—1·4382 (Griner, *Ann. Chim.*, 1892, [6], **26**, 347, gives b. p. 85—86°). There remained a small (*ca.* 10 g.) non-volatile brown residue.

Nona-1 : 5-*diyne* (IV).—Dipropargyl (14·6 g.) in dry ether (25 c.c.) was added during 15 minutes to a cooled (alcohol–carbon dioxide) and stirred suspension of sodamide in liquid ammonia (200 c.c.), prepared from sodium (4·7 g.) by the catalytic procedure. After 1 hour's stirring, propyl iodide (40 g.) in ether (40 c.c.) was added dropwise during 30 minutes, and the cooled mixture was then stirred for a further 6 hours. Ammonium chloride (*ca.* 15 g.) was introduced, the ammonia was evaporated on the steam-bath, and the product was isolated with ether. Distillation then gave *nona*-1 : 5-*diyne* (9·9 g., 44%) as a mobile pleasant-smelling liquid, b. p. 62°/19 mm., n_D^{20} 1·4562—1·4565 (Found: C, 89·65; H, 10·2. C_9H_{12} requires C, 89·9; H, 10·1%).

Nona-1 : 5-*diyne*-1-*carboxylic Acid* (V).—Nona-1 : 5-diyne (4·8 g.) in dry ether (10 c.c.) was added during 5 minutes to a stirred solution of ethylmagnesium bromide (from magnesium, 1·3 g.) in ether (80 c.c.) in an atmosphere of nitrogen. The solution was heated under reflux for 90 minutes and then cooled in ice. It was poured on to a large excess of solid carbon dioxide in a stainless-steel autoclave, which was then sealed and allowed to attain room temperature. After 14 hours the autoclave was opened, and the solid complex decomposed with dilute sulphuric acid. More ether was added, and the ethereal layer was washed with water and sodium hydrogen carbonate solution. The latter extract was washed with ether, acidified, and again shaken with ether. This last ether extract was dried and evaporated, yielding a residue which on cooling completely solidified. Crystallisation from light petroleum (b. p. 60—80°) gave *nona*-1 : 5-*diyne*-1-*carboxylic acid* (4·15 g., 63%) as plates, m. p. 85—86° raised to 87° by further crystallisation (Found: C, 73·45; H, 7·5. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%).

The experiment was also carried out similarly, except that the carboxylation with solid carbon

dioxide was at atmospheric pressure (*cf.* Part I, preceding paper). This yielded the crystalline acid (0·5 g., 8%), most of the starting material being recoverable.

Nona-1 : 5-diyne-1-carboxyl Chloride (VI).—The acid (V) (1·4 g.) and oxalyl chloride (3·0 g.) were heated under reflux for 30 minutes. The excess of reagent was removed under reduced pressure, and distillation of the residue gave the acid chloride (1·2 g.) as a pungent yellow liquid, b. p. 95—97°/0·8 mm., n_D^{20} 1·4930. There was a considerable brown solid residue. The distillation was found to be advisable as it facilitated the purification of the product obtained in the following stage.

N-isoButylnona-1 : 5-diyne-1-carboxyamide (VII).—A solution of *iso*butylamine (2·0 g.) in dry benzene (5 c.c.) was added dropwise during 5 minutes to the acid chloride (VI) (1·1 g.) in benzene (5 c.c.), with ice-cooling and continuous shaking. The clear solution was set aside at room temperature overnight, and was then washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried extract was evaporated, yielding a residue which completely solidified on cooling. One crystallisation from light petroleum (b. p. 40—60°) gave the *N-isobutylnona-1 : 5-diyne-1-carboxyamide* (1·02 g.) as long needles, m. p. 72° (Found: C, 76·3; H, 9·5; N, 6·5. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·65; N, 6·4%).

N-isoButylnona-1(cis) : 5(cis)-diene-1-carboxyamide (cis-cis-*Pellitorine*) (I).—The *N-iso*butyl-amide (0·81 g.) in ethyl acetate (15 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·08 g.; 5% Pd). Hydrogenation proceeded very rapidly and 2 moles of hydrogen (176 c.c. at 18°/778 mm.) were absorbed in *ca.* 5 minutes. The reaction was interrupted, the catalyst was filtered off, and the solvent was evaporated. Distillation of the residue gave cis-cis-*pellitorine* (0·61 g.) as a somewhat viscous colourless liquid, b. p. 125—126°/5 × 10^{-4} mm., n_D^{20} 1·4855—1·4857 (Found: C, 74·65; H, 11·3; N, 6·2. $C_{14}H_{25}ON$ requires C, 75·3; H, 11·3; N, 6·25%).

N-isoButylnonane-1-carboxyamide.—*cis-cis*-Pellitorine (0·12 g.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption was complete (26·5 c.c. of gas were absorbed at 23°/762 mm., equivalent to 2·0 H). Removal of catalyst and solvent, followed by crystallisation of the solid residue from light petroleum (b. p. 40—60°) at −40°, gave *N-iso*butylnonane-1-carboxyamide as a microcrystalline powder, m. p. 37—37·5° (Gulland and Hopton, *J.*, 1930, 6, give m. p. 36°).

Permanganate Oxidation of cis-cis-*Pellitorine* (I).—This oxidation was carried out with *cis-cis*-pellitorine (200 mg.) and potassium permanganate (750 mg.) in water (20 c.c.) in exactly the manner described by Jacobson (*J. Amer. Chem. Soc.*, 1949, **71**, 366) for natural pellitorine. The material not volatile in steam furnished *N-iso*butyloxamic acid (92 mg., 71%) as long needles, m. p. 103—104°, raised to 106—107° by another crystallisation (Jacobson, *loc. cit.*, gives 77% yield; m. p. 106—107°), and succinic acid (63 mg., 60%) as prisms, m. p. 186° undepressed on admixture with an authentic specimen (m. p. 189°) (Jacobson, *loc. cit.*, gives 69% yield). Titration of the steam-distillate with 0·1*N*-sodium hydroxide indicated that butyric acid had been obtained in 87% yield. It was identified as its *p*-bromophenacyl ester, m. p. 69° undepressed on admixture with an authentic specimen (m. p. 70°).

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26. *Complexes between Metal Salts and Long-chain Aliphatic Amines. Part I. The Complexes of Cupric Salts with Long-chain Amines.*

By A. R. Burkin.

Complexes between cupric salts and long-chain amines are described. The chain length affects only the solubility in organic solvents and physical properties of the complexes. The acid radical controls the colour and stability of the compounds, chelation leading to relative instability. The acid radicals are covalently bound to the metal. Cupric carbonate and oxide compounds are basic and decompose chloroform on heating, giving cupric chloride complexes.

The present work was carried out in order to study the relative stabilities, properties, and reactions of complexes of uni- and bi-valent copper salts and primary aliphatic amines with long carbon chains, dealing in particular with the effects of (*a*) the anion used, (*b*) the basicity of the amine, and (*c*) the nature of the solvent.

Water is generally used as the solvent in the study of copper complexes and it may have a considerable effect on the results obtained. In the case of cuprous compounds, this is often shown by a tendency to disproportionate, giving metallic copper and cupric ions. Bivalent copper has a great affinity for oxygen, and the properties of many cupric complexes are probably due to some extent to the partial replacement of the co-ordinating groups by water molecules. The tendency towards such aquation in the case of a salt $(MR_n)^{p+}\,X^-_p$ may be represented by equilibria of the types:

$$(MR_n)^{p+} \rightleftharpoons (MR_{n-1})^{p+} + R$$
$$(MR_{n-1})^{p+} + H_2O \rightleftharpoons (MR_{n-1}.H_2O)^{p+}$$

and in addition the anion present may co-ordinate according to the reaction

$$(MR_{n-1})^{x+} + X^- \rightleftharpoons (MR_{n-1}X)^{(x-1)+}$$

n being the normal chemical co-ordination number of the metal M, and R representing the ionically neutral monodentate ligand. The equilibrium position of the first reaction is determined by the normal stability constant of the complex ion and, in addition, more than one R group may be lost by the complex ion, leading to further equilibria involving water and the anion. The extent to which the last two groups enter the co-ordination sphere depends on the relative co-ordinating powers of R, H_2O, and X^-, on the nature of the metal M in the general case, and also on the energies of solvation of the various groups.

King (*J.*, 1930, 2307) studied cuprammonium salts and states that there is no evidence that aquation occurs when the complexes are dissolved in water. There is little evidence that it does not occur, however. He also presents some evidence suggesting that co-ordination of anions may occur to a small extent. Reversible co-ordination of anions is well established, however, since in addition to the obvious evidence presented by the methods of preparation of many complexes of cobalt, platinum, and other metals, containing acid radicals in the complex ion or molecule, King (*J.*, 1938, 1338; 1948, 1912) has shown that in the diammino- and triammino-platinous salts some acid radicals, normally regarded as present in the complex ions or molecules, ionise. This leads to the formation of aquated ammine ions in solution, although on crystallising, the original compounds are obtained. It is noteworthy that nitrate, sulphate, and picrate groups ionise in this way, while chloride remains in the complex molecule, diamminoplatinous chloride being practically a non-electrolyte.

In the present work the question of the influence of water does not arise, since the long-chain aliphatic amines used as ligands give complexes which are soluble in organic solvents such as chloroform, benzene, light petroleum, etc. This study of inorganic chemistry in inert organic solvents enables the properties of the actual complex molecules to be investigated and the effects of different acid radicals can thus be established.

The results obtained show that under these conditions the acid radicals are covalently bound to the copper atom and that the co-ordination number of 4 for copper is maintained. This behaviour is not observed for the copper complexes with lower amines, such as ethylamine, and ammonia, but it is believed that this is not the result of a fundamental change in the nature of the copper–acid radical links caused by changing the ligand from, say, ethylamine to *n*-octylamine, but is due to the solvents used. For example, cupric chloride with ethylamine gives complexes which are insoluble in organic solvents; the solids such as $CuCl_2(C_2H_5{\cdot}NH_2)_4$ are decomposed by water, giving a pale blue precipitate of basic cupric chloride containing a little ethylamine (or cupric hydroxide containing chloride and ethylamine which might be regarded as "adsorbed"). In aqueous ethylamine, however, the substances are soluble, and complex ions such as $[Cu(C_2H_5{\cdot}NH_2)_4]^{2+}$ may be presumed to be present. Octylamine, on the other hand, gives the *complex* $[CuCl_2(C_8H_{17}{\cdot}NH_2)_2]$, which is soluble in organic solvents and behaves as a complex molecule, but it is rapidly decomposed by water giving a pale blue precipitate containing chloride, and liberating octylamine.

All the cupric salts investigated gave bisamine complexes only, with long-chain amines, the acid radicals used being chloride, bromide, acetate, succinate, adipate, carbonate, sulphate, and that of methyl hydrogen succinate. Cupric chloride, acetate, and methyl succinate dissolve readily in a solution of 2 mols. of amine in a solvent, the bisamine complexes being precipitated on cooling to room temperature.

Cupric adipate and succinate give bisamine complexes which are unstable in solution in the absence of excess of amine. Adipic and succinic acids can form strainless rings on chelating with copper and the instability of the complexes is believed to be due to a reduction in the strength of the metal–amine bond caused by the imposition of the *cis*-configuration. The complex carbonates are also unstable and cannot be obtained without a considerable amount of associated amine carbonate.

Cupric sulphate is insoluble in solutions of the amines, but on adding the theoretical quantity of sulphuric acid to a solution of a lilac carbonate complex a pale blue precipitate of $(CuSO_4{\cdot}2C_{16}H_{33}{\cdot}NH_2)$ is deposited. This *complex* is insoluble in organic solvents, concentrated solutions of amines, and molten amine. A small amount of the same compound was obtained on heating copper sulphate with hexadecylamine at 160° for about 12 hours.

Addition of nitric acid to the carbonate solution caused decomposition to free amine and cupric nitrate, no complex being formed. Thus cupric nitrate complexes do not exist, and the sulphate compounds have exceptional insolubility. This may be due to nitrate and sulphate

radicals being less able to form covalent bonds to copper than the other groups used in this work. These same two anions were found by King (*loc. cit.*) to be less firmly bound to platinum than say Cl^-, tending to give aquated ions from $[Pt(NH_3)_2(NO_2)_2]$, etc.

Experimental.

The method used to prepare the complexes with the higher amines is essentially that of Broome, Ralston, and Thornton (*J. Amer. Chem. Soc.*, 1946, **68**, 67), the anhydrous cupric salt being dissolved in a solution of the amine in chloroform, benzene, light petroleum, etc., by boiling under reflux. On cooling, the complex separates and is purified by recrystallisation. Those authors and Ralston, Broome, Harriman, and Marcoux (*J. Amer. Oil Chem. Soc.*, 1947, **24**, 307) prepared the following compounds of cupric chloride, acetate, and oleate: $CuCl_2.2R{\cdot}NH_2$; $Cu(OAc)_2.2R{\cdot}NH_2$, and $Cu(C_{17}H_{33}{\cdot}CO_2)_2.2R{\cdot}NH_2$, where R is *n*-dodecyl or *n*-octadecyl. The former group of authors (*J. Amer. Chem. Soc.*, 1946, **68**, 849) also proved spectrophotometrically that complexes such as $Cu(OAc)_2.4R{\cdot}NH_2$ do not exist in solution.

In agreement with the above authors it was found that oxygen-containing solvents such as alcohols, ethers, and ketones give ill-defined greenish products which contain solvent and are deficient in acid radicals, so that compounds containing oxygen must not be used for either the preparation or the purification of the copper–amine complexes. Apart from this restriction, all the common organic solvents may be used, the choice being controlled, very largely, by solubilities, except in the case of the cupric carbonate complexes which are unstable except in benzene solution.

The amines used were *n*-octyl-, *n*-dodecyl-, *n*-tetradecyl-, *n*-hexadecyl-, and *n*-octadecyl-amine, and there was no difference between any of the cupric complexes as far as their type is concerned. The solubilities of the complexes differed considerably, however. Like many compounds possessing long carbon chains, the cupric bisamine complexes are very slightly soluble in cold solvents, and their solubility increases enormously over a very narrow temperature range, until they seem to be infinitely soluble at a slightly higher temperature (cf. Ralston *et al.*, *J. Org. Chem.*, 1944, **9**, 102). All the complexes prepared show this effect, the critical temperature region and range differing somewhat for different solvents and being higher the longer the carbon chain.

Cupric Chloride Complexes.—Cupric chloride (2·5 g.), dried at 110°, and *n*-octylamine (5·7 g., 2 mols.) were heated under reflux with 50 ml. of chloroform until solution was complete (½ hour). On cooling, the *complex* separated as a blue powder and was purified by recrystallising twice from chloroform (Found, in air-dried specimen: Cu, 16·1; Cl, 18·0. $C_{16}H_{36}N_2Cl_2Cu$ requires Cu, 16·2; Cl, 18·0%).

The following compounds were prepared similarly: $CuCl_2.2C_{12}H_{25}{\cdot}NH_2$ (Found: Cu, 12·7; Cl, 14·0. Calc. for $C_{24}H_{54}N_2Cl_2Cu$: Cu, 12·6; Cl, 14·0%). *Tetradecylamine* complex (Found: Cu, 11·15; Cl, 12·6. $C_{28}H_{62}N_2Cl_2Cu$ requires Cu, 11·2; Cl, 12·6%). *Hexadecylamine* complex (Found: Cu, 10·2; C, 11·6. $C_{32}H_{70}N_2Cl_2Cu$ requires Cu, 10·3; Cl, 11·5%). $CuCl_2.2C_{18}H_{37}{\cdot}NH_2$ (Found: Cu, 9·5; Cl, 10·6. Calc. for $C_{36}H_{78}N_2Cl_2Cu$: Cu, 9·4; Cl, 10·5%).

Anhydrous cupric chloride (2·0 g.) was gently warmed under reflux with 50 ml. of benzene containing anhydrous ethylamine (4 g., 6 mols.). The brown solid slowly absorbed ethylamine, turning blue and then purple, no solid dissolving. A further 10 g. of ethylamine were added, and a little purple solid dissolved, giving a deep blue solution. The solid was filtered off under suction and dried in a desiccator containing anhydrous ethylamine and petroleum jelly which absorbed benzene. Exposure to air caused loss of amine, the solid turning greenish-blue but reabsorbing gaseous amine and turning purple (Found: Cu, 19·2. Calc. for $C_4H_{22}N_2Cl_2Cu$: Cu, 20·2%).

Cupric Bromide Complexes.—Cupric bromide will dissolve only in the presence of about 3—4 mols. of amine, light petroleum being the most convenient solvent since the complex does not separate well from other solvents in the presence of the excess of amine. The evidence for the composition of the cupric bromide bisamine complexes is not entirely satisfactory since the copper content cannot be determined accurately by the methods used, the results usually being low and non-reproducible. The same effects are observed with the products obtained by oxidation of cuprous bromide compounds (Part III), so the original cupric bromide is not the cause. Heating the green complexes at 100—200° in high vacuum ($< 10^{-3}$ mm.) with no air leak causes amine to condense in the cold parts of the apparatus, the complex turning brown. This residue is still soluble in organic solvents, and addition of a little amine gives the original green solid, and although this must be free from excess of amine the copper figures are still low. The complex bromides are not volatile. The molecular weight of the *complex* ($CuBr_2.2C_{12}H_{25}{\cdot}NH_2$) determined ebullioscopically by the graphical method (Part II) in benzene is 990 ($C_{24}H_{52}N_2Br_2Cu$ requires *M*, 702). The high value compares with the value of 603 obtained for $CuCl_2.2C_{12}H_{25}{\cdot}NH_2$ as against the theoretical value of 505 (Ralston, Broome, and Thornton *loc. cit.*).

Anhydrous cupric bromide (3·0 g.) was boiled under reflux for 2 hours with octadecylamine (10·0 g., 2·8 mols.) and 50 ml. of light petroleum (b. p. 100—120°). The solid dissolved, giving a brownish solution (more amine gave green solutions) which turned green on cooling, depositing a green solid. This was recrystallised 3 times from light petroleum, the solution being filtered at 64°, and the green solid washed with several portions of fresh solvent. The product is apparently $CuBr_2.2C_{18}H_{37}{\cdot}NH_2$ (m. p. 116—117°) (Found: Cu, 6·8, 6·9; Br, 21·4, 21·4; C, 57·7; H, 10·8. $C_{36}H_{78}N_2Br_2Cu$ requires Cu, 8·3; Br, 20·95; C, 58·7; H, 10·3%). The analysis figures are the best obtained from many preparations, other amines giving such varied results that they are not quoted. After several recrystallisations a more soluble brown compound, apparently a cupric bromide complex containing less amine, could be obtained.

Cupric Acetate Complexes.—Cupric acetate was prepared by dissolving the commercial "neutral" salt in dilute acetic acid, filtering hot, cooling, and washing the crystals well with water and drying the air-dried solid *in vacuo* over phosphoric oxide until fresh desiccant extracted no more water. The anhydrous solid (1·1 g.) was boiled with octadecylamine (3·4 g.; 2·1 mols.) in 40 ml. of benzene for 30 minutes. The clear blue liquid on cooling gave a lilac solid which on recrystallising from benzene gave transparent lilac plates of $Cu(OAc)_2.2C_{18}H_{37}{\cdot}NH_2$, m. p. 89° (Found: Cu, 8·7; C, 64·6; H, 11·9. Calc. for $C_{40}H_{84}O_4N_2Cu$: Cu, 8·6; C, 66·6; H, 11·8%).

Cupric Methyl Succinate Complexes.—*Cupric methyl succinate* was prepared by boiling 50 g. of methyl hydrogen succinate with 30 g. (0·5 mol.) of cupric oxide and 50 ml. of water for 15 minutes. The considerable residue of cupric oxide was filtered off from the hot solution, which was cooled in ice, giving a mass of green crystals contaminated with excess of ester. The solid was dissolved in water with the minimum of heating, and the small amount of pale blue decomposition product filtered off from the hot solution. This was cooled rapidly in ice, and the green crystals were filtered off and dried in air and finally *in vacuo* over phosphoric oxide (Found : Cu, 19·50. $C_5H_7O_4Cu$ requires Cu, 19·50%).

Cupric methyl succinate (2·3 g.), octadecylamine (3·8 g.; 2·1 mols.) and 40 ml. of benzene were heated under reflux for 10 minutes. No solid separated from the clear blue liquid on cooling to room temperature, but on cooling in ice a blue solid separated. It was filtered off and recrystallised twice from benzene with rejection of the first third of the solid which separated in each case (this contained the excess amine). Pure *cupric methyl succinate bisoctadecylamine* was finally obtained (Found : Cu, 7·3. $C_{41}H_{82}O_4N_2Cu$ requires Cu, 7·35%).

Cupric methyl succinate bishexadecylamine was obtained similarly but was recrystallised from light petroleum (b. p. 60—80°) (Found : Cu, 9·05. $C_{37}H_{74}O_4N_2Cu$ requires Cu, 9·1%).

Cupric Succinate Complexes.—Cupric succinate was prepared by boiling cupric oxide in an aqueous solution of excess of succinic acid, filtering off the blue solid, and boiling it with more succinic acid solution. The crystals were dehydrated *in vacuo* over phosphoric oxide (Found : Cu, 35·7. Calc. for $C_4H_4O_4Cu$: Cu, 35·4%).

Cupric succinate (1·06 g.), octadecylamine (6·4 g., 4·2 mols.) and 80 ml. of benzene were heated under reflux for one hour. The boiling liquid was filtered, the filtrate cooled slowly, and the solid *complex* filtered off under suction at about 40°. It decomposed to cupric succinate on attempted recrystallisation, and amine impurity was removed by warming the lilac solid with benzene at about 45°, and filtering at that temperature. It was air-dried (Found : Cu, 8·73. $C_{40}H_{80}O_4N_2Cu$ requires Cu, 8·85%).

Cupric Adipate Complexes.—Cupric adipate was prepared as for the succinate (Found : Cu, 30·4. Calc. for $C_6H_8O_4Cu$: Cu, 30·6%). Its *bisoctadecylamine* complex was obtained as a lilac powder by the same method as the foregoing. It is insoluble in benzene and light petroleum in the absence of excess of amine, and is decomposed by boiling or long storage with these and all other solvents. Some of the product was very carefully recrystallised from chloroform. (Found : Cu, 8·8. $C_{42}H_{84}O_4N_2Cu$ requires Cu, 8·52%). The *bisdodecylamine* complex was obtained similarly but was purified only by washing with warm benzene (Found : Cu, 11·2. $C_{30}H_{68}O_4N_2Cu$ requires Cu, 11·0%).

Cupric Carbonate Complexes.—Copper oxide and hydroxide are completely unaffected by amine solutions in the absence of carbon dioxide, but in its presence they dissolve if about 4 mols. of amine are used, lilac cupric carbonate complexes separating on cooling. Benzene is the only suitable solvent of those tried, light petroleum giving only small quantities of a green complex oxide and chloroform being decomposed, the cupric chloride bisamine complex separating. The lilac complexes, including the insoluble ethylamine complex, are of the type $(CuCO_3,2R{\cdot}NH_2)[(R{\cdot}NH_2)_xCO_3]_{2-x}$, where x is variable between 0·7 and 2. Recrystallisation alters the value of x and must be done in the presence of gaseous carbon dioxide. If the solution is too hot or not enough carbon dioxide is present, a greyish-blue solid is obtained containing more copper and less carbon dioxide but of indeterminate composition, which absorbs carbon dioxide, turning lilac. The same blue products are obtained when lilac compounds are kept over soda–lime, etc., to remove carbon dioxide. Further loss of carbon dioxide from solutions of complex carbonates causes precipitation of green solids, very difficult to filter, the solution often setting to a gel on cooling. The green substances have the composition $(CuO,2R{\cdot}NH_2)$ but are contaminated with a slight excess of amine which could not be removed by solvents. They absorb carbon dioxide, turning lilac; there is no intermediate formation of a blue solid; the dodecylamine complex absorbs carbon dioxide much more readily than does the octadecylamine compound. The composition of the lilac complexes was proved by titration of a solution of $(CuCO_3,2C_{12}H_{25}{\cdot}NH_2)[(C_{12}H_{25}{\cdot}NH_2)_xCO_3]_{2-x}$ with alcoholic hydrogen chloride, a glass electrode and saturated calomel reference half-cell being used with a Marconi battery-operated pH meter. The pH titration technique was checked by titrating $(C_{12}H_{25}{\cdot}NH_2)_xCuCl_4$ with alcoholic sodium hydroxide.

Cupric hydroxide was prepared from cupric sulphate by Bullnheimer and Seitz's method (*Ber.*, 1900, **33**, 817) but was repeatedly washed and drained by filtration under suction instead of by decantation. It was free from chloride, sulphate, and soluble hydroxy-radicals, and was dried at 70° for 2 hours.

This hydroxide (1·36 g.) and dodecylamine (10·0 g., 4 mols.) in 75 ml. of benzene were heated under reflux for 12 hours with a soda–lime tube in the top of the condenser. There was no reaction. The soda–lime tube was removed, and the solution quickly turned blue, cupric hydroxide slowly dissolving. The reaction was more rapid when the solution was kept at 65—70° instead of being boiled, and dissolution was much faster when a current of carbon dioxide washed by saturated sodium hydrogen carbonate solution was bubbled through the suspension. Traces of solids were removed by filtering the liquid hot, and on cooling a lilac solid separated. The general method of preparation was to warm the benzene suspension in an open flask on a water-bath, carbon dioxide being passed in continuously until solution was almost complete. The lilac products were recrystallised from benzene. Too low a concentration of complex, too high a temperature, and too high a vacuum in the Buchner flask caused loss of carbon dioxide, blue and finally green solids being obtained. Carbon dioxide was passed through when the lilac compounds were being redissolved.

Dodecylamine gave a lilac *complex* (Found : Cu, 7·95; C, 66·2; H, 11·8%. $(CuCO_3,2C_{12}H_{25}{\cdot}NH_2)[(C_{12}H_{25}{\cdot}NH_2)_xCO_3]_{2-x}$ containing Cu, 7·95, requires C, 64·0; H, 11·8%). Recrystallisation from benzene gave another compound (Found : Cu, 8·20; C, 64·0; H, 11·4%).

A lilac compound was prepared from tetradecylamine but the solution was divided into two equal parts before cooling. The two crops of lilac powder were recrystallised from benzene under conditions as nearly as possible exactly similar (Found (i) : Cu, 6·40; CO_3^{--}, 12·3%; Cu : CO_3 = 1 : 2·03. Found (ii) : Cu, 5·85; CO_3^{--}, 12·7%; Cu : CO_3 = 1 : 2·30. $C_{15}H_{32}O_4N_2Cu$ requires Cu, 6·13; CO_3^{--}, 11·55%).

A lilac hexadecylamine complex was prepared as usual and recrystallised once from benzene. In one case the complex was *cupric carbonate bishexadecylamine–hexadecylamine carbonate* (Found : Cu, 5·54,

8·86; CO_3^{--}, 10·3. $C_{34}H_{100}O_3N_4Cu$ requires Cu, 8·53; CO_3^{--}, 10·4%). Attempts to repeat this preparation gave compounds with varying copper contents. Heating at 75° with carbon dioxide under pressure gave a complex (Found: Cu, 8·88%).

Octadecylamine gave similar *complexes* (Found, in one case: Cu, 5·70; C, 70·5; H, 12·3. $(CuCO_3,2C_{18}H_{37}\cdot NH_2)[(C_{18}H_{37}\cdot NH_2)_2CO_3]_2$ containing Cu = 5·70 requires C, 69·9; H, 12·5%).

Cupric hydroxide (3 g.) was warmed gently with ethylamine (large excess) in 50 ml. of benzene with a soda–lime tube in the top of reflux condenser; there was no reaction. On removal of this tube the cupric hydroxide slowly turned dark blue. When homogeneous in appearance it was filtered off under gravity, warmed gently with more ethylamine in benzene, under continuous passage of carbon dioxide, filtered off as before, washed with warm benzene, and dried in a desiccator containing anhydrous ethylamine carbonate and petroleum jelly in an atmosphere of carbon dioxide (Found: Cu, 24·3; CO_3^{--}, 31·2; $Cu:CO_3 = 1:1·36$. $(CuCO_3,2C_2H_5\cdot NH_2)[(C_2H_5\cdot NH_2)_2CO_3]_2$ containing Cu 24·3% requires CO_3^{--}, 30·3%). The *complex* lost ethylamine and carbon dioxide readily in air, turning green.

Blue cupric carbonate complexes are described by one typical example. A lilac cupric carbonate dodecylamine complex was recrystallised from benzene after being warmed to a higher temperature than usual, with no carbon dioxide passing. A blue solid was deposited (Found: Cu, 8·60; CO_3^{--}, 7·40%); after a further recrystallisation (Found: Cu, 8·91; CO_3^{--}, 7·60%). Analysis of a different preparation gave: Cu, 9·30; CO_3^{--}, 9·05 ($C_{25}H_{54}O_3N_4Cu$ requires Cu, 12·86; CO_3^{--}, 12·14%. $C_{49}H_{102}O_3N_4Cu$ requires Cu, 7·35; CO_3^{--}, 6·94%).

Cupric oxide bisoctadecylamine (impure) was obtained by boiling a lilac carbonate complex in benzene until it completely decomposed, giving a green suspension which set to a gel on cooling. The hot suspension was centrifuged; the green solid was washed three times with hot benzene, being centrifuged each time, and was dried in a vacuum desiccator containing soda-lime, under continuous pumping (Found: Cu, 8·93; CO_3^{--}, nil. $C_{72}H_{174}ON_4Cu$ requires Cu, 10·28%).

Cupric hydroxide (1·4 g.) and dodecylamine (10 g., 4 mols.) in 40 ml. of chloroform were heated under reflux for 2 hours. The blue solution gave a dark blue solid on cooling; this was recrystallised twice from benzene–light petroleum and once from benzene, and was found to be cupric chloride bisdodecylamine (Found: Cu, 12·1; Cl, 13·6. Calc. for $C_{24}H_{54}N_2Cl_2Cu$: Cu, 12·58; Cl, 14·04%).

Potentiometric Titration.—Cupric carbonate bishexadecylamine–hexadecylamine carbonate (p. 125) (0·2100 g.) was dissolved in 15 ml. of warm benzene and a mixture of 60 ml. of benzene and 15 ml. of redistilled commercial absolute alcohol added slowly at 40°, carbon dioxide being passed through the whole time. One drop of water was added. By this method, decomposition of the complex was avoided. The solution was titrated with 0·101N-hydrogen chloride in absolute alcohol, the course of the reaction being followed by a glass electrode and a saturated calomel half-cell with a ground-glass joint flowing junction. The e.m.f. was measured by means of a Marconi battery-operated pH meter (pH scale), previously standardised by using the same electrodes in an aqueous buffer at pH 6·46. The curve obtained is shown in Fig. 1 (I). The two sharp falls at 7·5 and 11·0 ml. of acid correspond to the addition of 4 and 6 equivs. of HCl per g.-mol. of complex. There is a significant flattening of the curve when 4 ml. (2 equivs.) of acid are present. The reaction proceeds in 3 stages, identified by the experiments described below:

(1) $CuCO_3,2C_{16}H_{33}\cdot NH_2 + 2HCl = CuCl_2,2C_{16}H_{33}\cdot NH_2 + H_2O + CO_2$
(2) $(C_{16}H_{33}\cdot NH_2)_2CO_3 + 2HCl = 2C_{16}H_{33}\cdot NH_2Cl + H_2O + CO_2$
(3) $CuCl_2,2C_{16}H_{33}\cdot NH_2 + 2HCl = (C_{16}H_{33}NH_3)_2CuCl_4$

Stage 1. 0·194 g. of lilac complex used in the titration was dissolved in 30 ml. of benzene, and alcoholic 0·101N-hydrogen chloride (3·5 ml., 2·0 equivs.) added slowly. The blue solid separating on cooling slightly was filtered off and recrystallised from benzene (Found: Cu, 10·1; Cl, 11·4. Calc. for $C_{32}H_{70}N_2Cl_2Cu$: Cu, 10·3; Cl, 11·6%).

Stages 1 + 2. 0·193 g. of lilac complex in 30 ml. of benzene was treated with 0·101N-hydrogen chloride (7·1 ml., 4 equivs.). The blue solid obtain on filtration was recrystallised from benzene and chloroform (Found: Cu, 10·2%).

Cupric Sulphate Complex.—0·1925 g. of a hexadecylamine cupric carbonate complex containing 4·42% of Cu was titrated with 0·101N-alcoholic sulphuric acid, with vigorous stirring, the reaction being followed as before. The 0·00851 g. of Cu = 2·64 ml. of the acid, and the 0·1113 g. of amine carbonate present = 4·03 ml. of acid. The experimental curve (Fig. 1, II) shows a slight break between 2·6 and 2·8 ml. and a distinct break at 6·7 ml. of acid added, corresponding to the formation of cupric sulphate bishexadecylamine and amine sulphate, respectively. There is no formation of a cuprisulphate (9·3 ml.).

Anhydrous copper sulphate is insoluble in solutions of amines. The lilac hexadecylamine complex used above (1·75 g.) was dissolved in 50 ml. of benzene, and 75 ml. of alcohol added, with passage of carbon dioxide. 0·101N-Alcoholic sulphuric acid (24·1 ml., $Cu:SO_4 = 1:1$) was run in slowly with stirring, and after standing overnight the pale blue *cupric sulphate bishexadecylamine* was filtered off. It was insoluble in organic solvents and molten amine, and was purified by extracting it several times with hot benzene (Found: Cu, 9·80. $C_{68}H_{140}O_4N_2SCu$ requires Cu, 9·90%).

Anhydrous copper sulphate (0·8 g.) was heated in a tube with excess of dodecylamine at 160° (oil-bath) for 40 minutes; the white solid then turned uniformly pale blue. The excess of amine was removed by extracting 4 times with hot benzene, giving *cupric sulphate bisdodecylamine* (Found: Cu, 11·9. $C_{24}H_{54}O_4N_2SCu$ requires Cu, 12·0%).

Double Cupribromides.—Cupric bromide bisoctadecylamine (1·0 g.) was dissolved in benzene, and excess of hydrobromic acid in aqueous alcohol added. Alcohol was added to the violet solution until the water which settled out redissolved. Dark violet *bisoctadecylamine cupribromide* which separated on cooling was filtered off and recrystallised from alcohol–benzene (Found: Cu, 6·85; Br, 34·3. $C_{36}H_{80}N_2Br_2Cu$ requires Cu, 6·90; Br, 34·7%).

Bishexadecylamine cupribromide (Found: Cu, 7·90. $C_{32}H_{72}N_2Br_2Cu$ requires Cu, 7·85%) and *bis-*

octylamine cupribromide (Found: Cu, 9·80. $C_{16}H_{36}N_2Br_4Cu$ requires Cu, 9·91%) were prepared similarly.

Double Cuprichlorobromides.—Alcoholic hydrogen chloride was added to a solution of cupric bromide bisoctadecylamine (1·0 g.) in benzene until the colour was orange. On standing, orange yellow *bisoctadecylamine cuprichlorobromide* separated and was recrystallised from benzene–alcohol (Found: Cu, 7·85. $C_{36}H_{76}N_2Cl_2Br_2Cu$ requires Cu, 7·60%). *Bisoctylamine cuprichlorobromide* was prepared similarly (Found: Cu, 11·30. $C_{16}H_{36}N_2Cl_2Br_2Cu$ requires Cu, 11·45%). The same orange yellow solids were obtained by treating the cupric chloride bisamine complexes with alcoholic hydrogen bromide. Excess of hydrogen bromide gave the violet cupribromides; and excess of hydrogen chloride with the cuprichlorobromides gave the yellow cuprichlorides.

FIG. 1.

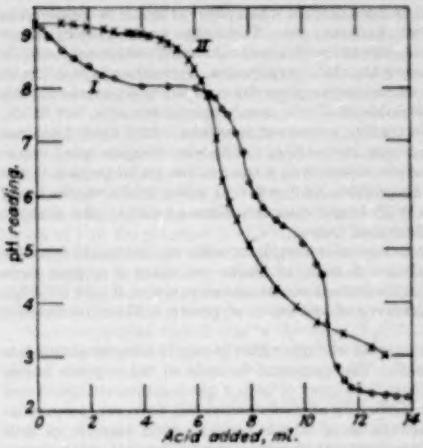
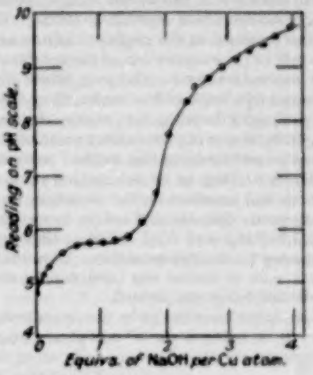


FIG. 2.



Double Cuprichlorides.—These were obtained by the methods of Ralston *et al.* (*loc. cit.*). Bistetradecylamine cuprichloride (0·1944 g.) in pure methanol (150 ml.) was titrated with 0·1183*N*-aqueous sodium hydroxide, the glass electrode assembly described under cupric carbonate complexes being used. The curve (Fig. 2) shows a sharp break when 2 equivs. of alkali are added, confirming the formulation as a double salt and the applicability of the glass electrode under such conditions.

The author's thanks are due to Armour & Co., Ltd., who supplied the octylamine and higher amines used.

UNIVERSITY COLLEGE, SOUTHAMPTON. [*Received, July 1st,* 1949.]

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27. *Complexes between Metal Salts and Long-chain Aliphatic Amines. Part II. The Complexes of Cuprous Halides with Long-chain Aliphatic Amines.*

By R. G. WILKINS and A. R. BURKIN.

Co-ordination compounds of cuprous salts (CuX) with long-chain aliphatic amines have been prepared and their structures investigated (*a*) by molecular-weight determinations and (*b*) by a study of their reactions. Cuprous chloride, bromide, and iodide form tetrameric monoamine complexes, $(CuX,R{\cdot}NH_2)_4$. Cuprous bromide forms also bisamine complexes which have dimeric bridged structures $(CuBr,2R{\cdot}NH_2)_2$ at low temperatures (freezing benzene) but dissociate into the monoamine complex and free amine at higher temperatures, the solid bisamine complex separating again on cooling. The preparation of the chloride and bromide was carried out in an oxygen-free atmosphere. Reaction between the monoamine complexes and pyridine gave, in all cases investigated, the cuprous halide–pyridine complex of empirical formula (CuX,C_5H_5N).

THERE is no work reported on complexes formed by co-ordination of higher primary aliphatic amines with cuprous salts. The amines chiefly used in the present work were *n*-octadecylamine,

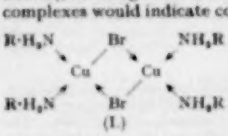
n-dodecylamine, and *n*-octylamine, hexadecylamine being used in a few cases where the fact that the stabilities and solubilities of its complexes are intermediate between those of the octadecyl- and the dodecyl-amine was of particular value. Cuprous chloride, bromide, and iodide were the metallic salts studied.

When cuprous chloride or bromide is added to a solution of about 2 equivs. of an amine in, for example, hot light petroleum, a mixture of blue and green, amine-containing, oxidation products is obtained. If, however, the reaction is carried out in the absence of oxygen, the cuprous salt gradually dissolves to give a green solution, which on cooling deposits a complex as a fine white or very pale green powder. A simple apparatus was devised for filtering off these compounds in the absence of air (see p. 130).

Cuprous iodide complexes are stable in air and are formed when cuprous iodide is dissolved in a hot solution of the amine in light petroleum, benzene, etc. The hexa- and octa-decylamine *complexes* are white crystalline solids. The *compounds* with lower amines are extremely soluble in the presence of the excess of amine necessary for their preparation, and either (*a*) cooling in ice-salt or (*b*) evaporation of the solution *in vacuo* merely gives the complex contaminated with the excess of amine. The pure solids are insoluble in all the usual organic solvents, but in the presence of a trace of free amine, they dissolve readily, giving red solutions, which turn colourless on prolonged heating, but regain their red colour on cooling. Molecular weights were determined by observing the boiling point of the solvent containing a trace of the amine present in the complex and treating this as the "solvent," the elevations due to the amine and complex being additive as long as no interaction occurs. With larger concentrations of amine, the amount present had an effect on the elevation, as is described below.

Cuprous chloride and iodide formed only monoamine *complexes* with the empirical formulæ $(CuCl,R{\cdot}NH_2)$ and $(CuI,R{\cdot}NH_2)$, although almost 2 mols. of amine per atom of copper were necessary for their preparation. Cuprous bromide formed a monoamine *complex*, $(CuBr,R{\cdot}NH_2)$, if one mol. of amine was used, but in the presence of two mols. of amine, a bisamine *complex* $(CuBr,2R{\cdot}NH_2)$ was formed.

No question arises as to the co-ordination number of copper for the cupric salt complexes (see Part I), it being 4 for all complexes examined. The empirical formula of the cuprous halide complexes would indicate co-ordination numbers for copper of both 2 (monoamine complex) and 3 (bisamine complex). In all cases examined, however, polymerisation occurs and the usual stable co-ordination number of 4 is attained. The bisamine complexes of cuprous bromide were shown by molecular-weight determinations in freezing benzene to have a dimeric, presumably bridged, structure (I; R = $C_{12}H_{25}$ and C_8H_{17}).



(I.)

The monoamine complexes were shown to have a tetrameric structure, as is described later. It is well established that halogen atoms can act as "bridging" groups between metallic atoms (for summary of work, see Mann, *Ann. Reports*, 1938, **35**, 151).

In boiling benzene solution the molecular weight found for the bisamine complexes did not correspond to either a monomeric or a dimeric structure. The observed elevation of boiling point did, however, correspond closely to the observed and calculated values caused by an equimolecular mixture of monoamine complex and amine. The same phenomenon was observed in *n*-hexane also. It is concluded therefore that at these slightly higher temperatures, the bisamine complex dissociated into the monoamine complex and free amine, but on cooling the solution the bisamine complex was precipitated again:

$$2(CuBr,2R{\cdot}NH_2)_4 \rightleftharpoons (CuBr,R{\cdot}NH_2)_4 + 4R{\cdot}NH_2$$

$$\downarrow py$$

$$4(CuBr,py) + 4R{\cdot}NH_2$$

Further evidence supporting this idea of dissociation is that when treated with 1 equiv. of pyridine in hot solvents, the bisamine complexes form monopyridinocuprous bromide, the same compound as is obtained when the monoamine complex is treated with pyridine.

The molecular weights of the monoamine complexes had to be determined ebullioscopically because of their insolubility in cold solvents. Cottrell's apparatus was used and a similar apparatus containing the solvent alone was employed as "reference" thermometer. This method of eliminating the influence of the barometer is more convenient and decidedly more accurate than any method involving barometer reading and the application of a correction. The determinations were carried out in a small, draught-free room, out of the sunlight, and the precautions

mentioned by Washburn and Read (*J. Amer. Chem. Soc.*, 1919, **41**, 729) were observed. The values for the boiling points were extremely steady and reproducible under these conditions, although the method is very sensitive to outside disturbances, so that any rapid movements by the observer appreciably altered the thermometer readings. In order to correct for the amount of solvent refluxing in the apparatus and present as vapour, and to smooth out the irregularities of individual readings, the solutions were progressively diluted and a number of observations made.

It can easily be shown that

$$C = 1000kC_1/\Delta T \cdot M + s \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where C is the weight of solvent introduced into the apparatus, C_1 is the weight of solute, and s is the weight of solvent "refluxing"—a constant depending on the size of the apparatus. From (1), the graph of the weight of solvent plotted against the reciprocal of the elevation is a straight line, of slope $1000kC_1/M$. The validity of the argument depends on the fact that the molecular weight is fairly constant over a range of concentrations. The straight lines obtained for a number of complexes when this graph is plotted support this contention.

All the cuprous halide monoamine complexes $(CuX,R{\cdot}NH_2)_x$ examined had values for x between 2·9 and 3·3. Their structures are presumably analogous to those of the complexes formed between cuprous iodide and trialkyl-phosphines or -arsines of empirical formulæ $CuI,P(\text{or As})R_3$: *X*-ray analysis of triethylarsine–cuprous iodide showed that the true molecule was $(CuI,AsEt_3)_4$ (Mann, Wells, and Purdie, *J.*, 1936, 1503). Mann, in addition, carried out a series of molecular-weight determinations on different members of the arsine and phosphine series in various solvents. Values of x in the polymer $(CuI,PR_3)_x$ were found in nearly all cases to lie between 3 and 4. It is possible that the low values of x are due to an inherent error in the molecular-weight determinations such as non-ideality of solution, the use of approximate formulæ, etc. It seems unlikely, however, that such a large and consistent difference is due to those causes and the more probable explanation is that some type of dissociation occurs in the solution.

Mann suggested that it was of the type $(R_3P,CuI)_4 \rightleftharpoons 4(R_3P,CuI)$, leading to a bicovalent cuprous complex. We have obtained, however, a certain amount of evidence for the following type of dissociation, at least with the cuprous iodide–amine complex:

$$(CuI,C_{18}H_{37}{\cdot}NH_2)_4 \rightleftharpoons (CuI,\overline{4-x}C_{18}H_{37}{\cdot}NH_2)_4 + 4xC_{18}H_{37}{\cdot}NH_2 \quad . \quad . \quad . \quad . \quad (2)$$

Thus we suggest that in hot solvents a small amount of amine splits off from the complex tetramer, but leaves the main bridged structure intact, a small proportion of the copper atoms momentarily having no amine attached. On cooling, the amine recombines once more and the original complex separates out. Quite a small degree of dissociation of this type, less than 10% of the amine molecules splitting off, would account for the observed results. The evidence for the type of dissociation postulated is as follows.

(1) Pure cuprous iodide–octadecylamine complex (compound *A*), was heated under reflux for about an hour in *n*-hexane in the presence of a small amount of dodecylamine. If octadecylamine had split off at all there should be competition between it and the dodecylamine when recombination occurred, and the product obtained on cooling and filtering (compound *B*) should contain dodecylamine and so have a higher copper content and lower carbon and hydrogen contents than the original compound *A*. Thus there is no question of any changes in analysis figures being due merely to contamination with excess of amine. The results obtained are given below and clearly indicate that a replacement of this type has occurred:

	$(CuI,C_{18}H_{37}{\cdot}NH_2)_4$ requires:	Compound *A*, found:	Compound *B*, found:
C, %	47·0	46·5	45·5
H, %	8·5	8·35	8·05
Cu, %	13·8	13·85	14·25

(2) When the molecular weight of the complex was determined in the presence of different amounts of octadecylamine, the observed value increased (corresponding to a decrease in the degree of dissociation) as the ratio of the amount of added amine to the amount of complex was increased. This would be expected, as the added amine would force the reaction (2) from right to left.

(3) On boiling a suspension of the pure complex in light petroleum in an open vessel for a few minutes, the solid lost a small amount of amine (which is slightly volatile in the solvent vapour), the copper content of the solid increasing from 13·85 to 14·2%. On recrystallising this from light petroleum containing just enough octadecylamine to make it soluble, the pure monoamine complex was obtained once more.

(4) Dissociation of this type is often encountered with co-ordination compounds of many different types. Thus most ammonia–cupric salt complexes lose ammonia very readily in air, and certain organic arsine complexes with metal salts are highly dissociated even in freezing benzene solution and smell strongly of the arsine, particularly the complexes of $IrCl_3$ with aryldialkylarsines (Dwyer and Nyholm, *J. Roy. Soc. N.S.W.*, **1944**, **77**, 116; **1946**, **79**, 121). Kharasch *et al.* (*J. Amer. Chem. Soc.*, **1938**, **60**, 882) obtained an approximate molecular weight of 409 for the styrene–$PdCl_2$ complex by the depression of the f.p. of benzene. This is intermediate between 282 for the monomeric and 564 for the dimeric form of $(PdCl_2,C_6H_5{\cdot}CH{:}CH_2)$ which should, by analogy with the $PtCl_2$ complex, be a bridged molecule. Instead of postulating splitting of the bridge, the value can be explained by assuming partial dissociation into free styrene.

We do not suggest that this type of dissociation explains all the observed phenomena of this type, for in the case of the cuprous iodide–trialkylarsine complexes the liberated trialkylarsine might be expected to oxidise easily and so lead to irreversible dissociation and decomposition of the complexes, which does not occur. Also, there is some evidence that dissociation into monomeric units also occurs. In the case of the reversible dissociation of the cuprous bromide bisamine complexes—presumably bridged dimers—into amine and cuprous bromide monoamine complexes—tetramers—it is difficult to see how the reaction can proceed except *via* the bicovalent monomeric units. As is shown in Part III, however, the mechanisms of reactions involving this type of complex in non-aqueous solvents are not clear, and dissociation giving free anions may also occur.

As mentioned above, the amine was readily replaced by a stronger co-ordinating group. Pyridine gave complexes with very low solubilities in organic solvents, thus making the determination of their molecular weights impossible. The compound obtained when cuprous iodide–amine complexes were treated with pyridine had an empirical formula (CuI,C_5H_5N). Varet (*Compt. rend.*, **1891**, **112**, 391) obtained the same substance as small yellow crystals by treating cuprous iodide with pyridine; when treated with ether, the substance became white, and when exposed to air, it became green and then brown, as observed by Varet (*loc. cit.*).

The monopyridinocuprous chloride complex, empirical formula $(CuCl,C_5H_5N)$, was obtained as a light yellow solid which rapidly turned green on exposure to air. In contrast to these substances, *monopyridinocuprous bromide* $(CuBr,C_5H_5N)$ was a white microcrystalline solid which showed no tendency to decompose and was extremely stable. This compound is not reported in the literature but $CuBr,2C_5H_5N$ is a well-known golden-green crystalline solid, decomposing rapidly in air (Varet, *Compt. rend.*, **1897**, **124**, 1156; Marukhyan, *J. Gen. Chem. Russia*, **1940**, **10**, 917).

The solubility of all the cuprous halide complexes in organic solvents decreased as the chain length of the amine involved increased. The cuprous chloride and bromide complexes, initially white solids, deepened in colour on storage in air, finally becoming a dark green. Their solutions, on boiling in air, undergo decomposition, and smell strongly of the amine.

Experimental.

General Method of Preparation of Complexes in an Inert Atmosphere.—In the preparation of all cuprous chloride and bromide complexes with amines, the same general method was employed. Variations in the reaction conditions are noted in the separate details of each experiment.

The whole apparatus (Fig. 1) was disconnected at the ground glass joint *A*, and the Buchner flask, funnel, and inlet tube were filled with the solvent to be used in the reaction. This was then displaced by passing a stream of nitrogen through the side-arm of the flask *B*, and allowing the solvent to pass out of the tube *C*. The side-arm and tube were closed and this portion of the apparatus was then placed on one side. The cuprous salt was placed in the reaction vessel *D*, and a stream of nitrogen was passed through the inlet tube *E* for about 15 minutes; this clears out any residual oxygen in the apparatus. The amine, dissolved in the solvent, was then added from the tap-funnel *F*, and the reaction allowed to continue until all the cuprous halide had dissolved (which indicated that the reaction was now complete), the nitrogen stream being continued meanwhile. The solution was cooled, and the complex then separated at a temperature which depended on the cuprous salt and amine used. The resultant solid was then filtered off in an atmosphere of nitrogen. The two separated parts were connected (as shown in Fig. 1), and the side-arm *B* connected to the water-pump. The filter-pump was then turned on, and the ground-glass joint *A* revolved 180°, whereupon the solid and solvent passed, *via* the glass joint and tubing, into the Buchner funnel. The solid was washed with solvent added from the tap-funnel *F*, and the precipitate then sucked dry for about 10 minutes. The Buchner funnel and precipitate were finally transferred quickly to a vacuum desiccator for final drying.

Determination of Molecular Weights.—Since the chloride and bromide complexes decomposed in air, when these complexes were used, the apparatus was filled with nitrogen, which had been washed by alkaline pyrogallol, dried by concentrated sulphuric acid, and saturated with solvent vapour. A slow stream of nitrogen was passed into the Cottrell's apparatus at the top of the condenser throughout the

determination, and the gas led away through about 4 feet of narrow tubing (2 mm.) to minimise back diffusion of air. The values obtained for the molecular weights are recorded below in separate sections, the graph number referring to Fig. 2.

In all the preparative work described below, light petroleum (b. p. 60—80°) was used, although the preparation of the complexes could also be carried out in other organic solvents, *e.g.*, benzene, in which they were much more soluble, the temperature of separation being correspondingly lower.

I. *Preparation of Cuprous Chloride Complexes.—With octadecylamine.* Cuprous chloride (0·9 g., 1 mol.) was heated with 100 ml. of light petroleum containing octadecylamine (5·0 g., 2·05 mols.) for an hour at 70—80°. The complex formed was soluble above about 67°, and the green solution formed was cooled to 55° and filtered. A light green solid *complex* was obtained, which turned dark green when left in air for about 10 days (Found: Cu, 17·34, 17·36, 17·24. $C_{18}H_{39}NClCu$ requires Cu, 17·24%). The analytical figures are for three separate preparations.

With dodecylamine. Cuprous chloride (1·3 g., 1 mol.) was heated with dodecylamine (5·0 g., 2·05 mols.) in 100 ml. of light petroleum for 20 minutes at 60—65°. The cuprous chloride dissolved and gave a dark green solution, which was filtered at about 40°, at which temperature the *complex* separated in large quantities. A white solid, it turned distinctly green within an hour (Found: C, 49·7; H, 9·5; Cu, 22·2; *M*, 2·9% solution in benzene, 590; 5·7% solution in benzene, 640. $C_{24}H_{102}N_4Cl_4Cu_4$ requires C, 50·7; H, 9·6; Cu, 22·4%; *M*, 1137).

Fig. 1.

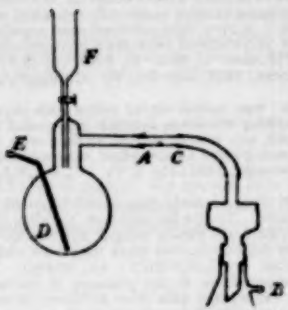
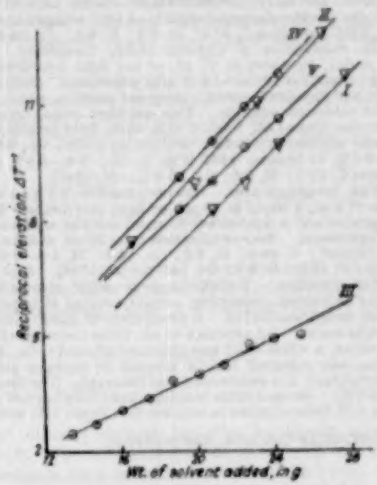


Fig. 2.



With octylamine. Cuprous chloride (1·2 g., 1 mol.) was treated with octylamine (3·2 g., 2·04 mols.) in 60 ml. of light petroleum at 60° for 15 minutes. A green solution was formed and this deposited a white solid on cooling, which must be a complex since octylamine is a liquid at these temperatures. Several attempts were made to filter it, but only a blue-green solid mixture was obtained.

With pyridine. The solution of cuprous chloride–octylamine in light petroleum, obtained as above, was treated with an excess of pyridine (1·0 g., 1·04 mols.). A yellow oil formed at the bottom and solidified on cooling to a yellow solid, which was filtered off in air. The yellow crystalline solid, on exposure to air, quickly turned green.

II. *Preparation of Cuprous Bromide Complexes.—With octadecylamine.* (i) Cuprous bromide (1·0 g.) was warmed with octadecylamine (2·0 g., 1·06 mols.) in 100 ml. of light petroleum at 55° for 20 minutes. The *complex* was filtered off at 20°. A white solid, it became dark green fairly quickly (Found: Br, 19·3; Cu, 15·45. $C_{18}H_{39}NBrCu$ requires Br, 19·35; Cu, 15·4%).

(ii) Cuprous bromide (0·77 g.) was treated with octadecylamine (3·0 g., 2·07 mols.) dissolved in 100 ml. of hot light petroleum. All the salt had dissolved in 10 minutes at 58°. The *bisamine*-complex was filtered off at about 50°. A white solid, it changed to a green solid very slowly (Found: Br, 11·8; Cu, 9·4. $C_{36}H_{79}N_2BrCu$ requires Br, 11·7; Cu, 9·3%).

With dodecylamine. (i) Cuprous bromide (1·0 g.) was warmed with dodecylamine (1·35 g., 1·05 mols.) in 100 ml. of light petroleum at 35—40° for 10 minutes; a light green solution was obtained. On cooling to 16°, the *complex* separated and was filtered off. The white solid quickly became green (Found: Br, 24·2; Cu, 19·3; *M*, 2·2% in hexane, 1970; 5·6—8·0% in hexane, 2040; 3·0—4·8% in benzene, 995 (see Fig. 2, I). $C_{24}H_{102}N_4Br_4Cu_4$ requires Br, 24·3; Cu, 19·3%; *M*, 1318). The graph obtained in n-hexane was not a straight line, indicating a change in *M* on dilution. The high value is difficult to interpret.

(ii) Cuprous bromide (1·0 g.) was warmed with dodecylamine (2·7 g., 2·1 mols.) in 150 ml. of light

petroleum at 45°; it dissolved within 5 minutes, and the *complex* began to separate at 38°. It was filtered off at 30°. The white solid slowly became green [Found: Br, 15·5; Cu, 12·4; *M* (cryoscopic), 2·9% in benzene, 1020; 2·8% in benzene, 1121; *M* (ebullioscopic), 3·9—7·5% in hexane, 650 (Fig. 2, III), 6·4% in benzene, 445. $C_{32}H_{268}N_4Br_2Cu_2$ requires Br, 15·5; Cu, 12·4%; *M*, 1040]. The ebullioscopic molecular-weight determinations in hexane and in benzene correspond closely to that required for an equimolecular mixture of the monoamine complex and amine.

With octylamine. (i) Cuprous bromide (1·0 g.) was treated with octylamine (1·0 g., 1·1 mols.) in 50 ml. of light petroleum at 25°. After about 5 minutes the copper salt had dissolved and the green solution was cooled in ice–salt. A white solid separated at −10°. It was filtered off and washed with ice-cold light petroleum. Little solid was obtained, it having apparently redissolved; it was very dark green.

(ii) Cuprous bromide (1·0 g.) was warmed with octylamine (2·0 g., 2·2 mols.) in 100 ml. of light petroleum. On warming above 40° for about 10 minutes, the salt dissolved to form a complex which gave a green solution. On cooling, the *complex* began to separate at 34° as a silvery-white solid [Found: Br, 19·65; Cu, 15·95; *M* (cryoscopic), 3·1% in benzene, 891. $C_{32}H_{72}N_4Br_2Cu_2$ requires: Br, 19·9; Cu, 15·8%; *M*, 804].

With pyridine. Pyridine (0·35 g., 1·1 mols.), dissolved in warm light petroleum, was added to a solution of cuprous bromide bisdodecylamine (2·0 g.) dissolved in 40 ml. of light petroleum at 40°. A feathery crystalline solid was deposited and filtered off while warm. It was washed with warm light petroleum and recrystallised from 20—30 ml. of light petroleum containing a little pyridine. A fluffy solid, the *complex* darkened rapidly at 130° without melting (Found: C, 26·9; H, 2·2; N, 6·8; Cu, 28·9. C_5H_5NBrCu requires C, 27·0; H, 2·3; N, 6·3; Cu, 28·6%).

III. *Preparation of Cuprous Iodide Complexes.—With octadecylamine.* Octadecylamine (0·95 g., 1·34 mols.), dissolved in 15 ml. of hot light petroleum, was added to a suspension of cuprous iodide (0·5 g., 1 mol.) in 10 ml. of hot light petroleum. Within about 15 minutes at 65°, in the air, the cuprous iodide had dissolved, giving a deep-red solution, which on continued heating under reflux changed to an almost colourless solution. This was then cooled to about 30°; a very light-coloured solid separated, which was filtered off, washed with warm light petroleum, and recrystallised twice from light petroleum. A white feathery crystalline *complex*, m. p. 98°, was obtained [Found: C, 46·5; H, 8·35; Cu, 13·8; *M*, 3·8—6·1% in hexane, 1492 (Fig. 2, II); 3·6—5·3% in benzene, 1332 (Fig. 2, IV). $C_{72}H_{144}N_4I_4Cu_4$ requires C, 47·0; H, 8·5; Cu, 13·8%; *M*, 1840].

With hexadecylamine. Hexadecylamine (2·8 g., 1·46 mols.) was heated under reflux with cuprous iodide (1·5 g., 1 mol.) in 60 ml. of light petroleum. The resulting colourless solution was cooled in a refrigerator and a light straw-coloured *complex* separated, which was filtered off and washed with cold light petroleum. Recrystallisation from 30 ml. of light petroleum yielded a pale yellow, microcrystalline solid [Found: C, 44·0; H, 8·3; Cu, 14·8; *M*, 4·0—6·1% in benzene, 1335 (Fig. 2, V). $C_{64}H_{136}N_4I_4Cu_4$ requires C, 44·5; H, 8·2; Cu, 14·7%; *M*, 1728].

With pyridine. Tetrakis(cuprous iodide octadecylamine) (1 g., 1 mol.) was dissolved in 50 ml. of light petroleum containing a small amount of octadecylamine. To the hot solution, pyridine (0·18 g., 1·05 mols.) was added. A precipitate of light feathery crystals was slowly formed, and was filtered off while warm. On exposure to air, these commenced to turn light green, but when they were washed with ether, a white solid was obtained (Found: Cu, 23·6. Calc. for C_5H_5NBrCu: Cu, 23·6%). The reaction was repeated with a solution of cuprous iodide–dodecylamine in the presence of excess of dodecylamine; a similar result was obtained. The final solid was washed with ether as before (Found: Cu, 23·7%). Several other reactions have been carried out on a solution of the complex between cuprous iodide and dodecylamine in solution (see Paper III) without the isolation of the solid complex.

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28. *Complexes between Metal Salts and Long-chain Aliphatic Amines. Part III. The Oxidation of Copper*(I) *Complexes to Copper*(II) *Complexes.*

By R. G. WILKINS and A. R. BURKIN.

Cuprous halide complexes with long-chain amines and with pyridine, having empirical formulæ CuX,Z, undergo aerial oxidation and in the presence of amine salts, Z,HX, form the corresponding cupric halide complexes, $CuX_2,2Z$, X representing the halogen atom and Z the ligand. The effect of changing X and Z is studied. The oxidation leads to the formation of hitherto undescribed complexes of cupric iodide with amines, $CuI_2,2R{\cdot}NH_2$. The mechanism of the reactions is not known.

AN interesting oxidation reaction, involving the cuprous salt amine complexes (Part II) and the cupric salt amine complexes (Part I) has been discovered and investigated. If tetrakis-[cuprous chloride (or bromide) monoamine], dissolved in a non-hydroxylic solvent such as benzene, chloroform, or *n*-hexane, was heated under reflux with the corresponding amine hydrochloride (or hydrobromide), then aerial oxidation occurred and a cupric chloride (or bromide) amine complex was formed (R = C_8H_{17}, $C_{12}H_{25}$, or $C_{16}H_{33}$; X = Cl or Br):

$$(CuX,R{\cdot}NH_2)_4 + 4R{\cdot}NH_2X\ (+\ 2O) \longrightarrow 4CuX_2,2R{\cdot}NH_2\ (+\ 2H_2O) \quad . \quad . \quad . \quad (A)$$

An analogous reaction was observed with the cuprous iodide amine complexes but it was very much slower and less complete, especially with the higher amines, *e.g.*, octadecylamine. These compounds are an interesting example of the stabilisation of an unusual valency state by co-ordination (cf. the formation of cupric iodide complexes with ethylenediamine; Morgan and Burstall, *J.*, 1926, 2018).

This type of oxidation reaction was shown to be fairly general for univalent copper salt complexes with amines. If the complex formed between one molecule of cuprous halide and one molecule of pyridine was treated with the corresponding pyridine salt, then dipyridinocupric halide was formed (X = Cl, Br, or I; py = pyridine):

$$2(CuX,py) + 2py,HX\ (+ O) \longrightarrow 2CuX_2,2py\ (+ H_2O) \quad . \quad . \quad . \quad . \quad . \quad (B)$$

(1) X = Cl. Dipyridinocupric chloride, $CuCl_2,2C_5H_5N$, is well known. Cox, Sharatt, Wardlaw, and Webster (*J.*, 1936, 129) prepared it in a number of ways in an unsuccessful attempt to obtain the *cis*-form. The product of this oxidation reaction was a blue microcrystalline solid, which recrystallised from methyl alcohol as fine, pale blue needles, exactly as described by Cox *et al.*, and was, without doubt, the *trans*-compound also.

(2) X = Br. The product of the oxidation reaction, dipyridinocupric bromide, $CuBr_2,2C_5H_5N$, was obtained by Pfeiffer and Pimmer (*Z. anorg. Chem.*, 1905, **48**, 98) as green needles, by direct reaction between the components.

(3) X = I. The reaction was extremely slow, and although it is believed (from colour changes of the solutions) that a small amount of oxidation occurred, no pure dipyridinocupric iodide was obtained, and large amounts of unchanged reactants were recovered.

By the use of this reaction, it was hoped to prepare a compound of the form (I), by an oxidation of the general type:

$$(CuX,R{\cdot}NH_2)_2 + 4R'{\cdot}NH_2Y\ (+ 2O) \longrightarrow 4\left[\begin{matrix} RNH_2 & & X \\ & Cu & \\ Y & & NH_2R' \end{matrix}\right]\ (+ 2H_2O)$$
(I.)

The investigation was divided into two stages: (i) changing the anion and using the same amine, and (ii) changing the amine and using the same anion. In reactions of type (i), disproportionation occurred and two products were formed (X = Cl, Y = Br or OAc; X = Br, Y = Cl or OAc; X = I, Y = Cl or OAc):

$$4\ (I) \longrightarrow 2\left[\begin{matrix} X & & NH_2R \\ & Cu & \\ RNH_2 & & X \end{matrix}\right] + 2\left[\begin{matrix} Y & & NH_2R \\ & Cu & \\ RNH_2 & & X \end{matrix}\right] \quad . \quad . \quad . \quad (C)$$
(II.) (III.)

Possibly the intermediate compound (I) is initially formed but this extremely quickly disproportionates to the products (II) and (III). The mechanism of the reaction is not clear, but must involve the breakage of a metal–halogen (or a metal–acetate) covalent bond. The two ways of effecting this are *via* (*a*) free radicals and (*b*) ions. The former is excluded since no halogenobenzene or phenyl acetate is formed when the reaction is carried out in benzene, unless it is postulated that the free radicals react much more quickly with each other than with benzene. Therefore the reaction involving ions must be explained on the idea that a small equilibrium concentration of ions is present in the non-polar solvents benzene or *n*-hexane. It is hoped to carry out conductivity measurements on the system in an attempt to detect such ions.

Broome, Ralston, and Thornton (*J. Amer. Chem. Soc.*, 1946, **68**, 849) carried out a spectrophotometric study of bisdodecylaminocupric acetate, $Cu(OAc)_2,2C_{12}H_{25}{\cdot}NH_2$, and showed that a 0·04M-solution in chloroform, at room temperature, dissociated into dodecylamine and cupric acetate to the extent of 10%. Further evidence for the comparatively loose attachment of the amine is shown by the fact that an analogous disproportionation reaction to the one described above, but now involving the co-ordinately-bound groups, has been observed; *e.g.*,

$$(CuCl,C_{12}H_{25}{\cdot}NH_2)_2 + 4C_8H_{17}{\cdot}NH_2Cl\ (+ 2O) \longrightarrow$$
$$4\left[\begin{matrix} Cl & & NH_2{\cdot}C_8H_{17} \\ & Cu & \\ C_{12}H_{25}{\cdot}NH_2 & & Cl \end{matrix}\right]\ (+ 2H_2O) \longrightarrow 2CuCl_2(C_{12}H_{25}{\cdot}NH_2)_2 + 2CuCl_2(C_8H_{17}{\cdot}NH_2)_2 \quad (D)$$
(IV.)

Small amounts of the intermediate compounds (I) and (IV) may be formed. These would

disproportionate easily, however, and their separation and identification would be extremely difficult.

The ease of oxidation depends on (*a*) the halogen and (*b*) the basicity of the amine. The complexes of cuprous chloride with amines and with pyridine are more rapidly and more completely oxidised than those of the bromide. The effect of the amine is most clearly shown when the cuprous iodide amine complexes are considered. About 40% of cuprous iodide dodecylamine is oxidised in the presence of dodecylamine acetate, when equimolecular proportions of the reactants are heated together in solution for 2 hours (Reaction C; X = I, Y = OAc, R = $C_{12}H_{25}$). The corresponding reaction involving hexadecylamine takes place to the extent of only about 5%, even when the reactants are heated under reflux in solution for 4 or more hours.

The heating together of tetrakis(cuprous iodide octadecylamine) with octadecylamine acetate for several days, in high-boiling solvents, does not result in appreciable reaction.

Cupric iodide bisdodecylamine was obtained, pure, as a dark brown waxy solid. The complexes of cupric iodide with hexadecylamine and octadecylamine were dark brown powders, which could not be obtained free from the reactants, since they were formed in such small amounts.

Experimental.

I. *Oxidation Reactions of Tetrakis(cuprous chloride alkylamines).*—In this section, the reactions of the octadecylamine complex are described as typical for all the other members of the series.

(*a*) *In the presence of octadecylamine hydrochloride* (*Reaction* A; X = Cl, R = $C_{18}H_{37}$). Freshly prepared cuprous complex (0·75 g., 1 mol.) was dissolved in 30 ml. of hot chloroform and added to octadecylamine hydrochloride (0·63 g., 1·05 mols.) dissolved in 20 ml. of hot chloroform. The hot green solution changed to blue almost immediately, and was heated under reflux for ½ hour. The solution was cooled and filtered at 45°. The solid deposited was recrystallised three times from chloroform. A blue powder, m. p. 125°, was obtained (Found: Cl, 10·6; Cu, 9·4. Calc. for $C_{54}H_{112}N_4Cl_4Cu$: Cl, 10·6; Cu, 9·4%). The reaction involving dodecylamine was carried out in a similar manner, and a blue solid was isolated, m. p. 124° (Found: Cl, 14·1; Cu, 12·6. Calc. for $C_{30}H_{64}N_4Cl_4Cu$: Cl, 14·05; Cu, 12·6%).

(*b*) *In the presence of octadecylamine acetate* (*Reaction* C; X = Cl, Y = OAc, R = $C_{18}H_{37}$). Cuprous chloride mono-octadecylamine (1·5 g., 1 mol.) was treated with octadecylamine acetate (1·08 g., 0·9 mol.) in 100 ml. of benzene. The green solution quickly changed to a deep blue colour, and was heated under reflux for 45 minutes and then cooled. A solid separated and was filtered off at about 35°; this was dark lilac-blue [fraction (i)]. The filtrate was dark blue and, when left overnight, deposited a lilac solid [fraction (ii)]. Fraction (i) was dissolved in 100 ml. of boiling benzene and cooled to 45°, at which temperature the solid was filtered off. It was recrystallised from 80 ml. of hot chloroform, giving a pale blue solid, m. p. 128° (Found: C, 64·8; H, 11·7; N, 4·2; Cl 10·6; Cu, 9·4. Calc. for $C_{36}H_{72}N_2Cl_2Cu$: C, 64·2; H, 11·7; N, 4·2; Cl, 10·6; Cu, 9·4%). Fraction (ii) was dissolved in 30 ml. of hot benzene and cooled. At about 45°, a solid separated which was filtered off at about 40°. Recrystallisation was repeated from 30 ml. of benzene. A lilac solid was obtained, m. p. 95° (Found: Cu, 8·8. Calc. for $C_{36}H_{68}N_2O_4Cu$: Cu, 8·8%). The reaction involving dodecylamine was carried out in a similar manner and two solids were obtained: blue, m. p. 124° (Found: Cl, 14·0; Cu, 12·5%), and lilac, transparent rectangular plates, m. p. 78° (Found: Cu, 11·1. Calc. for $C_{24}H_{48}O_4N_2Cu$: Cu, 11·8%). The reactions were also carried out in chloroform and in *n*-hexane with similar results.

(*c*) *In the presence of octylamine hydrochloride* (*Reaction* D). The cuprous complex (1·2 g., 1·0 mol.) was dissolved in 60 ml. of hot benzene and added to octylamine hydrochloride (0·43 g., 0·9 mol.) dissolved in 30 ml. of hot benzene. The hot green solution formed was heated under reflux for 45 minutes. It was then cooled; a solid separated at room temperature. This was filtered off and a light blue solid was obtained [fraction (i)] together with a green filtrate, which when left overnight deposited more blue solid [fraction (ii)]. Fraction (i) was recrystallised twice from 70 ml. of chloroform, the solid separating at about 45° being filtered off at 35° (Found: Cu, 9·1. Calc. for $C_{56}H_{72}N_4Cl_4Cu$: Cu, 9·4%). Fraction (ii) was not further treated (Found: Cu, 12·6. Calc. for $C_{16}H_{34}N_2Cl_2Cu$: Cu, 16·2%). Fraction (ii) appears to be a mixture of the two complexes of cupric chloride with octylamine and with octadecylamine; there is no doubt, however, that disproportionation occurs.

(*d*) *Oxidation of monopyridinocuprous chloride in the presence of pyridine hydrochloride* (*Reaction* B; X = Cl). Pyridinocuprous chloride (as prepared in Part II) was separated from the supernatant green liquid by decantation and dissolved in benzene (green solution). An excess (1·2 mols.) of pyridine hydrochloride dissolved in hot chloroform was added. The resulting dark solution quickly deposited a blue solid in large amounts. This was heated under reflux for a few minutes (the blue solid remaining insoluble) and then cooled. A light-blue micro-crystalline powder was filtered off. This was recrystallised from methyl alcohol, and fine pale blue needles were obtained (Found: Cl, 24·2; Cu, 21·9. Calc. for $C_{10}H_{10}N_2Cl_2Cu$: Cl, 24·2; Cu, 21·7%).

II. *Oxidation Reactions of Tetrakis(cuprous bromide alkylamines).*—The reactions of the octadecylamine complex are described as typical of those of all the cuprous bromide–amine complexes.

(*a*) *In the presence of octadecylamine hydrobromide* (*Reaction* A; X = Br, R = $C_{18}H_{37}$). Freshly prepared tetrakis(cuprous bromide octadecylamine) (1·0 g., 1 mol.) was dissolved in 25 ml. of warm benzene, and to it was added octadecylamine hydrobromide (0·85 g., 1 mol.) dissolved in 35 ml. of hot benzene. The resulting dark green solution was heated under reflux for about ½ hour, and then cooled to room temperature. A green solid was deposited, and the dark greenish-brown filtrate when left

overnight deposited a further amount of green solid. This was separated and recrystallised from 60 ml. of benzene. A solid separated on cooling, and was filtered off, washed with cold benzene, and dried. A light green solid, m. p. 114°, was obtained (Found: C, 57·2; H, 10·2; N, 4·0; Br, 21·1. Calc. for $C_{34}H_{73}N_2Br_4Cu$: C, 56·6; H, 10·3; N, 3·7; Br, 21·0%).

(*b*) *In the presence of octadecylamine hydrochloride* (*Reaction* C; X = Br, Y = Cl, R = $C_{18}H_{37}$). Tetrakis(cuprous bromide octadecylamine) (1·0 g., 1 mol.) was dissolved in 25 ml. of hot benzene, and octadecylamine hydrochloride (0·74 g., 1 mol.), dissolved in 35 ml. of benzene, was added. The dark green solution was heated under reflux for about 45 minutes, and then cooled. An apple-green solid separated and was filtered off. The dark green filtrate deposited more green solid when kept. The apple-green solid dissolved in 80 ml. of chloroform to give a dark green solution, which on cooling re-deposited solid, which was filtered off. This had a different shade of green colour, and if it was recrystallised a further three times from 30 ml., 30 ml., and 20 ml. of chloroform, respectively, a blue solid was obtained, m. p. 125° (Found: Cu, 9·4%). The filtrate deposited a green solid on each occasion, m. p. 113° (Found: Br, 21·3%).

(*c*) *In the presence of octadecylamine acetate* (*Reaction* C; X = Br, Y = OAc, R = $C_{18}H_{37}$). Tetrakis-(cuprous bromide octadecylamine) (1·0 g., 1 mol.) and octadecylamine acetate (0·82 g., 1·02 mols.), dissolved in 25 ml. and 30 ml. of hot benzene, respectively, were heated together under reflux for about 2 hours. The hot green-blue solution on cooling deposited first a green solid and then a small amount of lilac solid. The blue-green filtrate, on further storage, deposited more lilac solid. The green solid, recrystallised from benzene, had m. p. 113° (Found: Br, 21·0. Calc. for $C_{36}H_{73}N_2Br_4Cu$: Br, 21·0%). The lilac solid, recrystallised twice from small quantities of benzene (20 ml.), had m. p. 95° (Found: Cu, 9·3%).

(*d*) *Oxidation of monopyridinocuprous bromide in the presence of pyridine hydrobromide* (*Reaction* B; X = Br). Pure pyridinocuprous bromide (0·1 g., 1 mol.), suspended in benzene, was treated with a solution of pyridine hydrobromide (0·07 g., 1 mol.) in 15 ml. of benzene–alcohol. Most of the complex dissolved and on being heated under reflux for a short time, a deep-brown solution was formed, together with an insoluble green solid. The brown solution, on cooling, deposited more green solid, m. p. 142°. This solid gave, with excess of pyridine, hexapyridinocupric bromide, $CuBr_2,6C_5H_5N$, and with hydrobromic acid, reddish-black pyridinium cupribromide, $(C_5H_5N)_2CuBr_4$ (Pfeiffer and Pimmer, *loc. cit.*).

III. *Oxidation Reactions of Tetrakis(cuprous iodide alkylamines).*—(*a*) *Attempted reaction between tetrakis(cuprous iodide octadecylamine) and octadecylamine acetate* (*Reaction* C; X = I, Y = OAc, R = $C_{18}H_{37}$). A suspension of the cuprous iodide complex (0·5 g., 1 mol.) in 40 ml. of light petroleum (b. p. 80—100°) dissolved when octadecylamine acetate (0·36 g., 1 mol.) was added. The light-green solution was heated under reflux for several days (*a*) alone and (*b*) in the presence of excess of octadecylamine (to make the reaction conditions similar to those used in the dodecylamine work). The red solution finally obtained, on cooling, deposited first a white solid, m. p. 80—81° (m. p. of octadecylamine acetate 84°), and then unchanged cuprous complex.

(*b*) *Reaction between tetrakis(cuprous iodide hexadecylamine) and hexadecylamine acetate* (*Reaction* C; X = I, Y = OAc, R = $C_{16}H_{33}$). A solution of cuprous iodide monohexadecylamine (0·6 g., 1 mol.) in 30 ml. of light petroleum, containing a small amount of hexadecylamine, was heated under reflux with a solution of hexadecylamine acetate (0·4 g., 1·05 mols.) in 20 ml. of light petroleum. The initial green solution slowly became brown; after about 3 hours the solution was cooled, and a small amount of solid separated. This was filtered off, and a lilac solid was obtained; the brown filtrate on cooling continued to deposit a light-brown solid (a mixture of unchanged reactants and small amounts of the cupric iodide complex). When about 5—10 ml. of solution were left, no further solid separated and the brown solution on complete evaporation left a dark brown viscous solid, which on cooling in the refrigerator solidified and could be crushed to a brown powder, which however was not obtained pure.

(*c*) *Reaction between cuprous iodide dodecylamine and dodecylamine acetate* (*Reaction* C; X = I, Y = OAc, R = $C_{12}H_{25}$). Cuprous iodide (0·5 g., 1 mol.) was treated with dodecylamine (0·75 g., 1·4 mols.) in 40 ml. of light petroleum. After about 15 minutes, all the cuprous iodide had dissolved and a red solution was formed. To this hot solution, dodecylamine acetate (0·66 g., 1 mol.), dissolved in 30 ml. of light petroleum, was added, and the pale green solution formed was heated under reflux for 20 minutes. On cooling, this solution became dark green, but no solid was deposited. However, when it was left in an open dish for about 20 minutes, some solid was deposited. This was filtered off and a brown-lilac solid [fraction (i)] was obtained together with a green filtrate. This filtrate, on further storage, deposited more solid (lilac-brown, smelling strongly of free iodine) together with a dark brown filtrate which deposited no more solid, but left a dark brown, almost black, waxy solid [fraction (ii)] on complete evaporation. Passage of carbon dioxide through the dark brown light-petroleum solution precipitated, as the carbonate, any excess of amine remaining in solution at this stage. The limited solubility of the cupric acetate amine complex and the extreme solubility of the cupric iodide amine complex thus makes a very effective separation possible. Fraction (i) was dissolved in 30 ml. of hot benzene, and the blue solution kept for an hour in an open beaker, whereupon a crystalline solid was deposited. This was filtered off, washed, and dried, transparent, lilac, rectangular plates being obtained (Found: Cu, 11·1%). Fraction (ii), *cupric iodide bisdodecylamine*, was extremely soluble in organic solvents (Found: Cu, 9·3. $C_{24}H_{54}N_2I_2Cu$ requires Cu, 9·25%).

(*d*) *Reaction between cuprous iodide dodecylamine and dodecylamine hydriodide* (*Reaction* A; X = I, R = $C_{12}H_{25}$). Cuprous iodide-dodecylamine, in benzene solution (1·0 g., 1 mol.) (see preceding paragraph), was treated with dodecylamine hydriodide (0·8 g., 0·97 mol.) in 20 ml. of benzene, and the solution heated under reflux for 5 hours. The light-brown solution obtained, on cooling, became dark red, and finally brown-red. The solution was transferred to an evaporating dish and kept overnight; a dark brown, waxy solid, very similar to that obtained as described in paragraph (*c*), remained. The solution of the solid, in light petroleum, was cooled in a freezing mixture; some solid separated (dodecylamine hydriodide?) and was filtered off. Carbon dioxide was passed through the filtrate, and once more the solid was filtered off. The filtrate was evaporated to dryness. Analysis of the waxy residue indicated that it was the cupric iodide complex contaminated with unchanged dodecylamine

hydriodide and probably some iodine (Found: I, 43·5; Cu, 7·25. Calc. for $C_{14}H_{22}N_2I_4Cu$: I, 36·9; Cu, 9·25%).

Messrs. Weiler and Strauss, Oxford, carried out the microanalyses. Our thanks are due to Armour & Co. Ltd., for certain samples of amines, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. G. W.).

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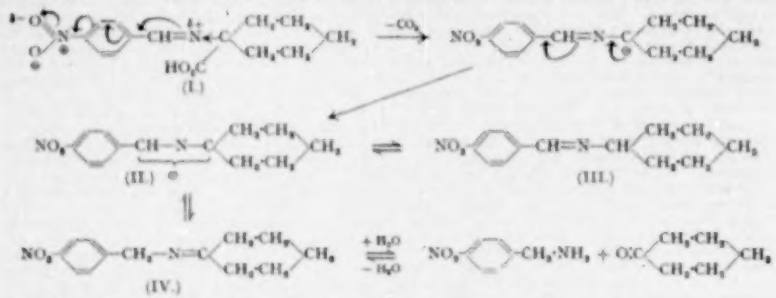
29. *Triad Prototropic Systems. Part I. The Mobility of the Azomethine System during Decarboxylation.*

By FAWZY G. BADDAR.

Whereas *p*-nitrobenzylidene-ethylamine and -cyclo*hexylamine*, and *o*-chlorobenzylidene-*cyclo*hexylamine and -ethylamine do not undergo tautomerism when refluxed with 50% glycerol or even dry pyridine, 1-amino*cyclo*hexane-1-carboxylic acid and alanine are readily degraded, when heated with *p*-nitro- or *o*-chloro-benzaldehyde in 75% pyridine, to *cyclo*hexanone and acetaldehyde, respectively. This shows that the anion (cf. II and VI) resulting from the decarboxylation of the corresponding azomethine-carboxylic acid (cf. I and V), which is supposed to be formed as an intermediate product, is more mobile than the corresponding azomethine (cf. III and VII). Further, ω-chlorobenzaldehyde and dichloroacetone degrade alanine and α-aminoisobutyric acid to acetaldehyde and acetone, respectively. In all cases the degradation is facilitated by replacing 50% glycerol by 75% pyridine.

IN a previous publication (Baddar, *J.*, 1949, S 163), the degradation of α-amino-acids by certain carbonyl compounds was interpreted electronically. According to this interpretation the degradation can be effected by any carbonyl compound, in which the carbonyl group is preferably directly attached to, or conjugated with, strong electron-attracting groups. The azomethine systems are known to be immobile (cf. Ingold and Piggott, *J.*, 1922, **121**, 2381) and tautomerism in these systems requires strong nucleophilic reagents such as sodium ethoxide (cf. Ingold, Shoppee, and Thorpe, *J.*, 1926, 1477; Ingold and Shoppee, *J.*, 1929, 1199). The degradation of α-amino-acids with certain carbonyl compounds is supposed to take place by the condensation of the carbonyl compound with the α-amino-acid to give an azomethine-carboxylic acid (cf. I), which is then decarboxylated to an intermediate anion (cf. II). This, owing to its mobility, can combine with a free proton to give a mixture of the two possible tautomerides (cf. III and IV).



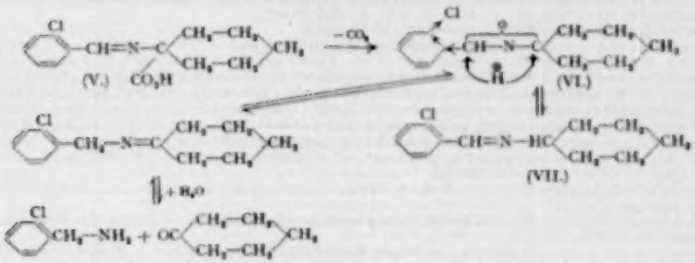
In the present investigation the author made a comparative study of the effect of decarboxylation on the mobility of these systems. It was found that, whereas certain azomethines are immobile even in presence of strong nucleophilic reagents such as sodium ethoxide, the system becomes mobile, even in presence of a weak nucleophilic reagent such as pyridine, if decarboxylation is expected to take place as an intermediate step. Thus, whereas, *p*-nitrobenzylidene-ethylamine, and -*cyclo*hexylamine (III) gave practically no acetaldehyde or *cyclo*hexanone respectively when refluxed with 50%-glycerol or even with dry pyridine, alanine (cf. Baddar, *loc. cit.*) and 1-amino*cyclo*hexane-1-carboxylic acid gave, when refluxed with 50% glycerol, acetaldehyde, and *cyclo*hexanone respectively.

Similarly, whereas *o*-chlorobenzylidene-*cyclo*hexylamine (VII) and -ethylamine did not undergo tautomerism when refluxed with dry pyridine or, in the case of the former compound, with

alcoholic sodium ethoxide, 1-amino*cyclo*hexane-1-carboxylic acid and alanine were degraded with *o*-chlorobenzaldehyde, when heated with 75% pyridine, to *cyclo*hexanone and acetaldehyde respectively.

If the azomethine-carboxylic acids (I) and (V) are formed as intermediate products and the ionic nature of decarboxylation is accepted (cf. Brown and Hammick, *J.*, 1949, 173), the corresponding azomethine-carboxylate ions afford on decarboxylation the mesomeric azomethine anions (II) and (VI) respectively. This naturally requires much less energy than that necessary for the extraction of a proton from the azomethine systems (III) and (VII).

o-Nitrobenzaldehyde with 1-amino*cyclo*hexane-1-carboxylic acid gave an indigo-blue compound, but no *cyclo*hexanone was isolated. The nature of this compound, as well as those similarly obtained from alanine and α-amino*iso*butyric acid (cf. Baddar, *loc. cit.*), is under investigation. The yield of *cyclo*hexanone liberated from 1-amino*cyclo*hexane-1-carboxylic acid with *m*-nitrobenzaldehyde was much less than that with *p*-nitrobenzaldehyde. This supported the previous assumption by Baddar (*loc. cit.*) that in *m*-nitrobenzaldehyde the nitro-group operates only by its relatively weak inductive effect ($-I$), whereas, in *p*-nitrobenzaldehyde it operates by both its inductive ($-I$) and its strong tautomeric ($-T$) effect.



In *o*-chlorobenzaldehyde the chlorine atom appears to operate only by its strong inductive effect ($-I$), thus effecting the decarboxylation of the azomethine-carboxylic acid (V) and enhancing the mesomeric shift of electrons in the intermediate anion (VI). The electromeric effect ($+E$) of the chlorine atom appears not to operate in this degradation, as the yield of acetaldehyde and acetone liberated from alanine and α-amino*iso*butyric acid, respectively, by *o*-chlorobenzaldehyde was slightly higher than that liberated by *m*-chlorobenzaldehyde under the same conditions.

The above observations, however, add a further proof to the ionic nature of prototropy (cf. Ingold, Shoppee, and Thorpe, *loc. cit.*; Ingold and Shoppee, *loc. cit.*; Shoppee, *J.*, 1931, 1225).

The degradation of alanine and α-amino*iso*butyric acid to acetaldehyde and acetone respectively was effected also by *s*-dichloroacetone in boiling water. The yield increased when water was replaced by 50% glycerol. This showed that the effect of glycerol in increasing the yield is not merely to aid dissolution or wetting but is probably caused by its higher boiling point and its greater nucleophilic character. Under similar conditions *s*-dichloro*iso*propyl alcohol failed to effect this degradation. This showed that the carbonyl group in *s*-dichloroacetone is involved, probably by a mechanism similar to that mentioned above. In *s*-dichloroacetone the two chlorine atoms exert more electron-attraction on the system than the one chlorine atom in the chlorobenzaldehydes, and thus cause an easier degradation.

Experimental.

The degradation of α-amino-acids was carried out as mentioned by Baddar (*loc. cit.*). The liberated carbonyl compounds were identified as their 2 : 4-dinitrophenylhydrazones. Yields are reproducible within ±10%, although they are of no quantitative significance as the hydrazones were contaminated with traces of those of the original carbonyl compounds.

Degradation of Alanine with o- and m-Chlorobenzaldehyde.—(i) *o*-Chlorobenzaldehyde (0·46 g., 1 mol.) and alanine (0·3 g., 1 mol.) were heated on a boiling water-bath with 75% pyridine (20 c.c.) in a carbon dioxide atmosphere for 3 hours. The liberated acetaldehyde was precipitated as its 2 : 4-dinitrophenylhydrazone (*ca.* 0·09 g.) (Found: C, 43·2; H, 3·7; N, 24·8. Calc. for $C_8H_8O_4N_4$: C, 42·9; H, 3·6; N, 25·0%), which was crystallised from alcohol and identified by its m. p. and mixed m. p. with an authentic specimen.

(ii) The experiment was repeated using *m*-chlorobenzaldehyde, and the liberated acetaldehyde was

precipitated as its 2 : 4-dinitrophenylhydrazone (*ca.* 0·065 g.) and identified as above (Found: N, 25·4, 24·8%).

When the degradation was carried out with *o*-chlorobenzaldehyde (0·46 g.) in 50% glycerol [*cf.* Baddar, *loc. cit.*], only *ca.* 0·01 g. of acetaldehyde 2 : 4-dinitrophenylhydrazone was collected, which after two crystallisations was identified as above.

Degradation of Alanine with s-Dichloroacetone.—A mixture of dichloroacetone (0·64 g., 1 mol.), alanine (0·6 g.), and water (20 c.c.) was refluxed in a carbon dioxide atmosphere for 3 hours. The precipitated hydrazone (*ca.* 0·07 g.) was crystallised from dilute alcohol and identified as above (Found: C, 42·9; H, 3·6; N, 24·3%).

When water was replaced by 50% glycerol, the yield of acetaldehyde enormously increased. Pyridine could not be used as it appeared to react with dichloroacetone.

α-Aminoisobutyric acid, when similarly treated, gave acetone.

Under similar conditions *s*-dichloroisopropyl alcohol failed to effect the degradation of alanine.

Degradation of α-Aminoisobutyric Acid with o- and m-Chlorobenzaldehyde.—A mixture of the chlorobenzaldehyde (0·46 g., 1 mol.), α-aminoisobutyric acid (0·35 g., 1 mol.), and 75% pyridine (20 c.c.) was heated for 3 hours as above.

(i) With *o*-chlorobenzaldehyde, the precipitated derivative (*ca.* 0·1 g.) was crystallised from dilute alcohol and identified as acetone 2 : 4-dinitrophenylhydrazone (Found: C, 45·5, 45·3; H, 4·1, 4·3; N, 23·0. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2, N, 23·95%), by its m. p. and mixed m. p. with an authentic specimen.

(ii) With *m*-chlorobenzaldehyde, the precipitated acetone 2 : 4-dinitrophenylhydrazone (*ca.* 0·55 g.) was identified as above (Found: C, 45·8; H, 4·3; N, 23·5, 23·4%).

With 50% glycerol practically no acetone was liberated.

Degradation of 1-Aminocyclohexane-1-carboxylic Acid with p- and m-Nitrobenzaldehyde.—The amino-acid (0·5 g., 1 mol.) and the nitrobenzaldehyde (0·5 g., 1 mol.) were heated with 50% glycerol (20 c.c.) for 3 hours in a carbon dioxide atmosphere. Water was added and the product distilled in a carbon dioxide atmosphere. The distillate was treated with a solution of 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitated derivative was extracted with boiling alcohol, filtered from the insoluble derivative of the nitrobenzaldehyde, diluted with water, and allowed to crystallise. In case of *p*-nitrobenzaldehyde, the yield of the crystalline derivative was about 0·15 g., and was identified as *cyclo*hexanone 2 : 4-dinitrophenylhydrazone by m. p. and mixed m. p. (Found: C, 51·7, 52·0; H, 5·2, 5·0; N, 20·6, 20·1. Calc. for $C_{18}H_{18}O_4N_4$: C, 51·8; H, 5·0; N, 20·1%).

With *m*-nitrobenzaldehyde, traces of the *cyclo*hexanone derivative were isolated and were identified by m. p. and mixed m. p.

o-Nitrobenzaldehyde gave an indigo-blue compound but practically no *cyclo*hexanone came over on distillation (*cf.* Baddar, *loc. cit.*).

Degradation of 1-Aminocyclohexane-1-carboxylic Acid with o-Chlorobenzaldehyde.—A mixture of *o*-chlorobenzaldehyde (0·3 g.), the α-amino-acid (0·3 g.), and 75% pyridine (20 c.c.) was treated as above. The reaction mixture was acidified with dilute hydrochloric acid and distilled. The distillate was treated with 2 : 4-dinitrophenylhydrazine hydrochloride, the precipitated derivative extracted with hot alcohol, and the solution filtered. The filtrate was diluted with water and allowed to crystallise. The product was recrystallised from dilute alcohol and identified by m. p. and mixed m. p. as *cyclo*hexanone 2 : 4-dinitrophenylhydrazone. The fraction insoluble in alcohol crystallised from acetic acid in orange-red crystals, m. p. 208·5—209·5°, undepressed on admixture with an authentic specimen of *o*-chlorobenzaldehyde 2 : 4-dinitrophenylhydrazone.

When the degradation was carried out in 50% glycerol instead of 75% pyridine, practically no *cyclo*hexanone was liberated.

o-Chlorobenzylidene-ethylamine.—*o*-Chlorobenzaldehyde (5·0 g.) was treated with anhydrous ethylamine (6 c.c.) in the cold. Heat was evolved and the aldehyde dissolved. The mixture was left overnight at room temperature, diluted with water, and extracted with ether. The *o-chlorobenzylidene-ethylamine* was dried (Na_2SO_4) and distilled, to give a colourless oil, b. p. 84·5°/3 mm. (Found: C, 64·4; H, 6·0; N, 8·0, 8·3; Cl, 21·4, 21·5. $C_9H_{10}NCl$ requires C, 64·5; H, 6·0; N, 8·4; Cl, 21·2%). It was soluble in dilute hydrochloric acid, and decomposed to give the original aldehyde on warming.

p-Nitrobenzylidenecyclohexylamine (III).—An ethereal solution of *p*-nitrobenzaldehyde (1 g.) and *cyclo*hexylamine (0·66 g.) was set aside overnight. The ethereal solution was washed with 2% acetic acid and with sodium hydrogen carbonate solution, and then dried (Na_2SO_4). Evaporation of the ether left a *benzylidene* derivative (*ca.* 1·5 g.), which crystallised from light petroleum (b. p. 60—70°) in colourless prismatic needles, m. p. 85·5—86° (Found: C, 67·4, 66·9; H, 6·9, 6·9; N, 11·8, 12·2. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

o-Chlorobenzylidenecyclohexylamine (VII).—An ethereal solution of *o*-chlorobenzaldehyde (2·8 g.) and *cyclo*hexylamine (2·0 g.) was treated as above. The dry product was distilled in a vacuum, to give *o-chlorobenzylidenecyclohexylamine* as a colourless oil, b. p. 135—136°/3 mm. (*ca.* 3·8 g.) (Found: C, 70·0, 70·6; H, 7·0, 7·3; N, 6·4, 6·3; Cl, 16·5, 15·6. $C_{13}H_{16}NCl$ requires C, 70·4; H, 7·2; N, 6·3; Cl, 16·0%). It dissolved in dilute hydrochloric acid and decomposed on warming.

p-Nitrobenzylidene-ethylamine.—A mixture of *p*-nitrobenzaldehyde (0·5 g.) and 30% aqueous ethylamine (4 c.c.) was heated for few minutes on a water-bath. The mixture was diluted with water, and the precipitated *product* (0·55 g.) was filtered off and crystallised from light petroleum (b. p. 60—70°) in colourless silky needles, m. p. 76—77° (Found: C, 61·0, 60·7; H, 5·7, 5·4; N, 15·4, 15·5%; *M*, 178. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·6; N, 15·7%; *M*, 178).

Tautomerism of o-Chlorobenzylidene-ethylamine.—(i) When *o*-chlorobenzylidene-ethylamine (0·5 g.) was heated with 50% glycerol (20 c.c.) for 3 hours in a carbon dioxide atmosphere, practically no acetaldehyde was liberated. A similar result was obtained when glycerol was replaced by dry pyridine and the mixture refluxed for 6 hours, followed by acidification with dilute sulphuric acid and distillation in a carbon dioxide atmosphere.

(ii) The azomethine (0·5 g.) was refluxed with alcoholic sodium ethoxide (1 g. of sodium in 20 c.c. of

absolute alcohol) for 5 hours. The solution was acidified with dilute sulphuric acid, and the liberated acetaldehyde was driven off by a stream of carbon dioxide. An appreciable amount of acetaldehyde 2 : 4-dinitrophenylhydrazone was collected and identified by its m. p. and mixed m. p. However, a similar result was obtained when the experiment was repeated with ethylamine itself.

Tautomerism of p-*Nitrobenylidene-ethylamine and -cyclohexylamine.*—The azomethines were refluxed with 50% glycerol or dry pyridine as stated above. The product was acidified with dilute sulphuric acid and distilled. Practically no acetaldehyde or *cyclo*hexanone was obtained.

Tautomerism of o-Chlorobenzylidenecyclohexylamine.—The azomethine was similarly refluxed with 50% glycerol, dry pyridine or sodium ethoxide. The acidified solution was distilled, and the distillate treated with 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitated derivative was extracted with hot alcohol, and the extract filtered, diluted with water, and allowed to crystallise. The precipitated product, *o*-chlorobenzaldehyde 2 : 4-dinitrophenylhydrazone (trace), melted at 200—202°.

M. p.s are not corrected. Microanalyses were carried out by Drs. Weiler and Strauss of Oxford.

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30. *Colchicine and Related Compounds. Part IX.*

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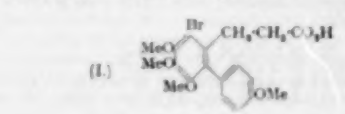
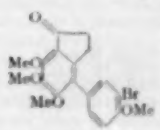
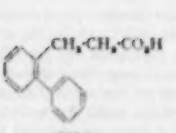
In Part V (*J.*, 1945, 176) it was shown that a degradation product of colchicine, deamino-colchinol methyl ether, is a derivative of dibenz*cyclo*heptatriene, and a synthesis of this parent hydrocarbon was described in Part VI (*J.*, 1947, 746). The present communication records the preparation and cyclisation of *β-2-diphenylylpropionic acid* (III) and some of its derivatives with a view to determine whether this type of method is adaptable to the synthesis of dibenz*cyclo*heptadiene derivatives related to colchicine. In agreement with the conclusions of von Braun and his collaborators, the main product of cyclisation of (III) was found to be *4-phenylindanone* (IV), but there was also formed, albeit in yields of less than 10%, the seven-membered ring ketone (V). The cyclisation of various methoxylated derivatives of (III) was also examined, but in no other case was evidence of seven-membered ring formation obtained. The ketone (V) was also synthesised from diphenic acid. Poor yields at an early stage discouraged attempts to extend the method to the synthesis of derivatives of (V).

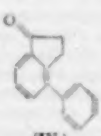
Observations are recorded on the desulphuration of thiol esters of some aromatic acids by means of Raney nickel.

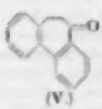
THE course, (I) ⟶ (II), taken by the Friedel–Crafts reaction when applied to the acid chloride of (I) (Barton, Cook, and Loudon, Part VIII, *J.*, 1949, 1079; Huang, Tarbell, and Arnstein, *J. Amer. Chem. Soc.*, 1948, **70**, 4181) is probably determined by a combination of orienting influences and steric factors. Considered from the point of view of cyclisation to a 7-membered ring, the methoxylation pattern is unfavourable: in particular, the position of the methoxyl group in the disubstituted nucleus is unfortunate, since the directive powers of the substituent are not enlisted to offset the steric difficulty which is implicit in the rule that, *ceteris paribus*, a 5-membered ring is formed in preference to a 7-membered ring. Because of the importance of dibenz*cyclo*heptadienones in the chemistry of colchicine we have now investigated the direction of ring-closure in several compounds related to (I).

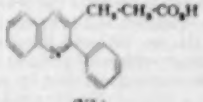










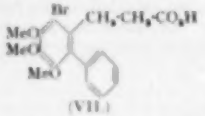


Von Braun and Manz (*Annalen*, 1929, **468**, 258) have reported that the indanone (IV) is the sole product of cyclising (III) by the Friedel–Crafts reaction. Their conclusion, however, is based on very unconvincing evidence: the indanone (IV) is described as an oil, alleged to be homogeneous because it afforded a sharp-melting semicarbazone (no analyses are given), and

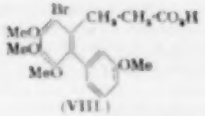
identified only through oxidation with nitric acid which appeared to yield a nitrated derivative of phthalic acid as judged from a qualitative nitrogen test and a fluorescein reaction. For re-investigation, diphenyl-2-aldehyde was conveniently prepared from the acid by the McFadyen–Stevens process (*J.*, 1936, 584) and was condensed with malonic acid to β-2-diphenylylacrylic acid (cf. Zaheer and Faseeh, *J. Indian Chem. Soc.*, 1944, **21**, 381). Hydrogenation of the latter acid using a palladium catalyst gave the required β-2-*diphenylylpropionic acid* (III) which, however, was markedly different from the compound described by von Braun *et al.* Repetition of the method of preparation used by these authors, and based on the condensation of 2-bromomethyldiphenyl (here obtained by an alternative method) with ethyl sodiomalonate, showed that the properties which they ascribe to (III) correspond with the properties now found for (*2-diphenylylmethyl*)*malonic acid*. The latter acid, when heated, afforded a sample of (III) which was identical with the material produced by our first method of preparation.

Cyclisation of (III) by the Friedel–Crafts reaction gave a crystalline solid as main product, together with some oil. The solid was identified as 4-*phenylindanone* (IV) by oxidation with potassium permanganate to 3-phenylphthalic acid and conversion of the latter into fluorenone-1-carboxylic acid of which an authentic specimen was available. A portion of the oil was oxidised with sodium dichromate in acetic acid, and the formation of phenanthraquinone and of diphenic acid clearly indicated the presence of some dibenz*cyclo*heptadienone (V) (cf. Part VI, Cook, Dickson, and Loudon, *J.*, 1947, 746). This was confirmed when the remainder of the oil was treated with 2 : 4-dinitrophenylhydrazine and, from the resulting mixture, the 2 : 4-dinitrophenylhydrazone of (V) was isolated. The total quantity of (V) in the cyclisation product was small—less than 10%.

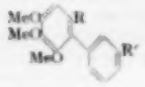
As an alternative to the Friedel–Crafts type of cyclisation, the action of anhydrous hydrogen fluoride on the acids (I) and (III) was examined. By this means (III) was again converted into a mixture of (IV) and (V), the presence of the latter being inferred from the isolation of phenanthraquinone following oxidation. Frank, Fanta, and Tarbell (*J. Amer. Chem. Soc.*, 1948, **70**, 2314) state that (I) does not undergo cyclisation when treated with hydrogen fluoride, but we now find that it affords a mixture of (II) and the debrominated indanone (II; H for Br), apparently formed by displacement and either migration or elimination of the bromo-substituent. Accordingly, in the respective cases, the Friedel–Crafts and the hydrogen fluoride method of cyclisation appear to produce essentially similar results and, when applied to (I), the latter method has the advantages of giving more easily separable products in better total yield (cf. Part VIII, *loc. cit.*). The production of (V) from (III) encourages the hope that dibenz*cyclo*heptadienones may be synthesised by this method when favourable orienting influences are present, but it is relevant to add that Borsche and Sinn (*Annalen*, 1939, **538**, 283) were unable to obtain the 7-membered cyclic ketone by cyclisation of (VI) although in this case a 5-membered ring was not formed.



(VII.)



(VIII.)



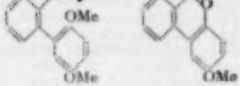
(IX; R = CO_2H, R' = H.) (X; R = CO_2H, R' = OMe.)
(XI; R = CHO, R' = H.) (XII; R = CHO, R' = OMe.)
(XIII; R = CH:CH·CO_2H, R' = H.) (XIV; R = CH:CH·CO_2H, R' = OMe.)
(XV; R = $CH_2·CH_2·CO_2H$, R' = H.) (XVI; R = $CH_2·CH_2·CO_2H$, R' = OMe.)

In order to ascertain whether the position of the methoxyl group in the disubstituted nucleus materially affects the course of the reaction (I) ⟶ (II), the two *acids* (VII) and (VIII) were synthesised and examined. The syntheses followed the lines already described for (I) (Part VIII, *loc. cit.*) and involved condensations of 1-phenyl- and 1-m-*methoxyphenyl*-3 : 3-*dimethyltriazen* with methyl 3 : 4 : 5-trimethoxybenzoate to form the *methyl* esters of the *acids* (IX) and (X) respectively (for by-products, cf. Experimental). Cyclisation of these acids by warming with thionyl chloride yielded *fluorenone* derivatives, a pair of isomers which were not individually oriented being obtained from the acid (X). Reduction of (IX) and (X) to the respective *aldehydes* (XI and XII) and subsequent conversion into the acrylic (XIII and XIV) and propionic *acids* (XV and XVI) were effected by standard methods. Bromination of (XV) and (XVI) gave the *bromo-acids* (VII) and (VIII), respectively. On cyclisation with hydrogen fluoride each of the acids (XV) and (XVI) gave a corresponding *indanone* derivative, and the failure of the

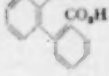
cyclisation products to furnish (coloured) phenanthraquinones in the oxidation test indicated the absence of dibenz*cyclo*heptadienones. The same test was again negative when applied to the cyclisation products of the bromo-acids (VII) and (VIII). The former acid, when cyclised by either the Friedel–Crafts or the hydrogen fluoride method, gave only gummy products which were probably mixtures. On the other hand, (VIII) was cyclised by hydrogen fluoride to a brominated *indanone* which, on debromination, afforded 5 : 6 : 7-*trimethoxy*-4-m-*methoxyphenyl*-*indan*-1-*one*, already obtained by direct cyclisation of (XVI). Accordingly, it may be concluded that, in this case at least, cyclisation is achieved by displacement and migration of bromine, and that in neither case is there any significant tendency to form a 7-membered ring.

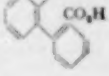
It is noteworthy that the displacement and migration of bromine, encountered in these cyclisations to indanone derivatives, finds its counterpart in the isomerisation which accompanies cyclisation of β-(9-*s*-octahydroanthranyl)propionic acid to 1′-keto-9 : 10-*cyclo*penteno-*s*-octahydrophenanthrene (Badger, Carruthers, Cook, and Schoental, *J.*, 1949, 169). In the latter case it is a saturated carbon chain which migrates, and in both types hydrogen fluoride is an effective agent.

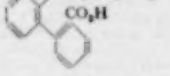
2′ : 5′-*Dimethoxydiphenyl*-2-*carboxylic acid* (XVII), prepared through the *methyl* ester by condensing 1-(*o*-carbomethoxyphenyl)-3 : 3-dimethyltriazen and 1 : 4-dimethoxybenzene, was next examined in the hope of applying the synthetic procedure to a case favourable to 7-membered ring formation. The project, however, failed since the ester was recovered unchanged from all attempts to convert it by reaction with hydrazine hydrate into the hydrazide. Moreover, even mild treatment of (XVII) with thionyl chloride yielded the *lactone* (XVIII) of 2′-hydroxy-5′-methoxydiphenyl-2-carboxylic acid.


(XVII.)

(XVIII.)


(XIX.)


(XX.)


(XXI.)

A different approach to the synthesis of the unsubstituted ketone (V) was made starting from diphenic anhydride. This reacted with hydrazine hydrate to form the half hydrazide of diphenic acid, which with benzenesulphonyl chloride afforded the N-*benzenesulphonyl* derivative. The latter was also obtained by the direct action of benzenesulphonhydrazide on diphenic anhydride and by an adaptation of the McFadyen–Stevens process gave the *aldehydo-acid* (XIX) in rather poor yield. Condensation of (XIX) with malonic acid yielded an unsaturated dibasic acid (XX) which was hydrogenated by use of a palladium catalyst to the corresponding saturated acid (XXI). From this acid by heating (*a*) the barium salt alone or (*b*) the sodium salt with acetic anhydride there was obtained in each case a gum which afforded the 2 : 4-dinitrophenylhydrazone of (V). The method, however, is inferior to the synthesis of (V) recently reported by Rapoport and Williams (*J. Amer. Chem. Soc.*, 1949, **61**, 1774) who prepared the same acid (XXI) in several stages from phenanthraquinone mono-oxime and achieved a more satisfactory cyclisation through the corresponding dinitrile by means of Ziegler's procedure.

In course of the foregoing synthetic work the frequent need of reducing a carboxylic acid to the corresponding aldehyde prompted some investigation of reductive desulphuration of thiolcarboxylic esters by means of Raney nickel. Wolfrom and Karabinos (*J. Amer. Chem. Soc.*, 1946, **68**, 1455) report the formation of aldehydes in this way, whilst Prelog *et al.* (*Helv. Chim. Acta*, 1946, **29**, 684) recommend the process for the preparation of primary alcohols. The results of our experiments show the prevalence of reduction beyond the aldehyde stage as well as the incidence of side reactions, but the activity of the catalyst may well be the critical factor determining the nature of the product (cf. Spero, McIntosh, and Levin, *J. Amer. Chem. Soc.*, 1948, **70**, 1907) and requires further inquiry. Previous workers have confined their attention to thiol esters derived from methane-, ethane-, or toluene-ω-thiol, but it seems probable that in many cases these malodorous thiols may be replaced by thiophenols such as thio-*p*-cresol which was mainly used in the present connection.

By use of Raney nickel as prepared by Mozingo (*J. Amer. Chem. Soc.*, 1943, **65**, 1015) the half *thiol-ester* from diphenic anhydride and thio-*p*-cresol was converted into 2′-hydroxymethyldiphenyl-2-carboxylic acid, and p-*tolyl* o-*carbomethoxythiolbenzoate* [o-$C_6H_4(CO_2Me)$·CO·S·C_7H_7] yielded phthalide. A test experiment on *p*-tolyl thiolbenzoate showed the formation of benzaldehyde (*ca.* 10%) and benzyl alcohol (23%); moreover, examination of the more volatile

products from ethyl thiolbenzoate revealed unexpectedly the presence of much benzene. Both *ethyl* and *p-tolyl* **3 : 4 : 5-*trimethoxythiolbenzoate*** afforded **3 : 4 : 5**-trimethoxybenzyl alcohol (40%) together with **1 : 2 : 3**-trimethoxybenzene (20—30%) and the formation of these products was largely independent of the conditions or of the thiol-ester used. The results, therefore, show that scission of the original carboxyl group may accompany desulphuration and reduction, and it may be recalled that similar competitive processes have been noted in connection with the Rosenmund reduction of acid chlorides (Späth, *Monatsh.*, 1919, **40**, 129; Rosenmund, Zetzsche, and Heise, *Ber.*, 1921, **54**, 638) where again the activity of the catalyst is of paramount importance.

Experimental.

Diphenyl-2-aldehyde from the 2-Carboxylic Acid.—Methyl diphenyl-2-carboxylate (14·8 g.), heated under reflux with hydrazine hydrate (98%; 25 g.) and ethanol (30 c.c.) for 5 hours, afforded the *hydrazide*, as colourless needles, m. p. 136·5°, from methanol (Found: C, 73·8; H, 5·6. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7%). The product (9·6 g.) in pyridine (40 c.c.) was treated at 0° with benzenesulphonyl chloride (8·2 g.) and the whole was left for 3 hours at room temperature before it was added to a mixture of ice and hydrochloric acid. The resulting *benzenesulphonhydrazide* of diphenyl-2-carboxylic acid formed colourless needles, m. p. 173·5°, from methanol (Found: C, 64·8; H, 4·6. $C_{19}H_{16}O_3N_2S$ requires C, 64·8; H, 4·6%). A solution of the above sulphonhydrazide (14·3 g.) in ethylene glycol (70 c.c.) was treated at 160° with anhydrous sodium carbonate (21 g.) and after 90 seconds the reaction was quenched by pouring the mixture into hot water. The required aldehyde, recovered in ether, had b. p. 162°/12 mm.; the yield was 55%, based on the acid.

1-o-Tolyl-3 : 3-dimethyltriazen.—*o*-Toluidine (32·1 g.) in concentrated hydrochloric acid (108 c.c.) and water (72 c.c.) was diazotised at 0° with a concentrated aqueous solution of sodium nitrite (21 g.) and the resulting solution was added with stirring to an ice-cold solution of dimethylamine (33%; 48 g.) in 30% aqueous sodium carbonate (300 c.c.). The required *triazen*, b. p. 128—129°/12 mm., was recovered from a dried and washed benzene extract (Found: C, 66·1; H, 7·8. $C_9H_{13}N_3$ requires C, 66·3; H, 8·0%).

2-Methyldiphenyl was obtained in poor yield by the following procedure: Glacial acetic acid (40 c.c.) was gradually added to a boiling solution of the above triazen (45 g.) in benzene (400 c.c.) and the whole was heated under reflux for 16 hours. The resulting solution was washed in turn with water, dilute hydrochloric acid, dilute alkali, and again with water. Fractionation of the dried benzene solution gave 2-methyldiphenyl, b. p. 128—130°/15 mm. (9%), and neutralisation of the acid washings gave indazole (21%), m. p. 144—145° (Found: C, 71·5; H, 5·0; N, 23·8. Calc. for $C_7H_6N_2$: C, 71·2; H, 5·1; N, 23·7%).

2-Bromomethyldiphenyl was prepared in 65% yield by adding (2 hours) a solution of bromine (4·1 g.) in carbon tetrachloride (12 c.c.) to a strongly irradiated, boiling solution of 2-methyldiphenyl (4·1 g.) in the same solvent (25 c.c.) which contained a trace of iodine and was covered with a layer of water (6 c.c.). After further heating (½ hour), the cooled solution was washed in turn with sulphurous acid, dilute sodium carbonate, and water before being dried and concentrated. The required product distilled at 168—172°/11 mm. (von Braun and Manz record b. p. 166°/12 mm.).

(2-Diphenylylmethyl)malonic Acid.—The corresponding diethyl ester, prepared as described by von Braun and Manz (*loc. cit.*), was hydrolysed by potassium hydroxide in boiling ethanol–water. After distillation of the ethanol and extraction of the diluted solution with ether, the aqueous residue was acidified and the precipitated oil was extracted with much boiling water from which the *acid* slowly crystallised, having m. p. 125·5—127·5° (decomp.); it was dried at 65° *in vacuo* (Found: C, 71·1; H, 5·1. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

β-2-Diphenylylpropionic Acid (III).—(*a*) β-2-Diphenylylacrylic, m. p. 196°, prepared essentially as described by Zaheer and Faseeh (*loc. cit.*) who give m. p. 202°, was dissolved (6·2 g.) in glacial acetic acid (450 c.c.) and was hydrogenated using palladium-black as catalyst (0·3 g.) at ordinary temperature and pressure. Absorption was complete in 2½ hours and the product, recovered from the solvent, had m. p. 110—113°. Methylation with diazomethane in ether gave the *methyl* ester, b. p. 181·5—182°/10 mm. (Found: C, 80·1; H, 6·5. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%), from which the *acid* was recovered by hydrolysis and formed plates, m. p. 112·5—113°, from aqueous acetic acid (Found: C, 79·8; H, 6·0. $C_{15}H_{14}O_2$ requires C, 79·7; H, 6·2%). (*b*) The same acid, m. p. and mixed m. p. 111—113°, was obtained when 2-diphenylylmethylmalonic acid was heated at 130° until evolution of carbon dioxide ceased and the product was crystallised from benzene–petroleum.

4-Phenylindanone (IV).—β-2-Diphenylylpropionic acid (2 g.) suspended in pure dry benzene (20 c.c.) was treated with phosphorus pentachloride (2 g.), shaken until solution of the acid was complete, and left at room temperature for one hour. The acid chloride, recovered after evaporation under reduced pressure, was dissolved in dry carbon disulphide (4 c.c.), powdered aluminium chloride (3 g.) was added, and the whole was left protected from moisture at 0° for 3 days. Dilute hydrochloric acid was added and after distillation in steam to remove the solvent the residual liquor was extracted with ether from which, when washed with dilute alkali, dried, and evaporated, a gum was recovered. The gum distilled at 130—135°/10 mm. (yield 75%) and crystallised in the receiver; recrystallisation from ethanol–water gave rectangular prisms of *4-phenylindanone* (yield 45%), initially melting at 69°, but changing on storage to m. p. 86° (Found: C, 86·7; H, 5·6. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%), while the mother-liquor of the crystallisation was worked up as described below. 4-Phenylindanone formed a 2 : 4-*dinitrophenylhydrazone* (referred to as "A" below) as scarlet needles, m. p. 243—245° (decomp.), from acetic acid (Found: C, 65·1; H, 4·3. $C_{21}H_{16}O_4N_4$ requires C, 65·0; H, 4·1%), and a *semicarbazone* as colourless platelets, m. p. 225—229° (decomp.) from 2-ethoxyethanol (von Braun and Manz, *loc. cit.*, record m. p. 192°) (Found: C, 72·3; H, 5·6; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·9%).

Oxidation. A well-stirred emulsion of the indanone (IV) (0·2 g.) in a little dilute sodium hydroxide

at 100° was treated portionwise with 6% aqueous potassium permanganate until the pink colour persisted. Excess of permanganate (2 c.c.) was now added and the whole was maintained at 100° for 1 hour. After acidification and treatment with sulphur dioxide the insoluble product was collected, washed with water, reprecipitated from alkali, and again collected. Sublimation at 120°/2 mm. furnished *3-phenylphthalic anhydride*, m. p. 145°, from benzene–petroleum (Found: C, 74·9; H, 3·5. $C_{14}H_8O_3$ requires C, 75·0; H, 3·6%), from which 3-phenylphthalic acid, m. p. 169—171°, was obtained on hydrolysis (Heilbron *et al.*, *J.*, 1938, 1386, give m. p. 181°). For identification, the latter was cyclised by warming for 10 minutes in concentrated sulphuric acid from which dilution with water yielded fluorenone-1-carboxylic acid, m. p. and mixed m. p. with an authentic specimen 190—191°, from ethanol–water.

Detection of Dibenzocycloheptadienone (V).—The mother-liquor from the crystallisation of 4-phenylindanone gave a colourless gum on evaporation. (i) One portion of the gum (0·3 g.) in acetic acid (3 c.c.) was heated under reflux for 1 hour with a solution of sodium dichromate (1·3 g.) in acetic acid (3·5 c.c.). A chloroform extract of the diluted solution was washed with aqueous sodium hydroxide, dried, and concentrated. The gummy neutral residue gave crystals of phenanthraquinone, m. p. and mixed m. p. 204—205°, from chloroform (diazine, from *o*-phenylenediamine, m. p. and mixed m. p. 216—219°). The alkaline liquor gave, on acidification, diphenic acid, m. p. and mixed m. p. 216—219°. (ii) The residual gum (0·28 g.) was treated with 2 : 4-dinitrophenylhydrazine (0·3 g.) in ethanol–sulphuric acid and the well-washed precipitate was dissolved in the minimum quantity of hot acetic acid. On cooling, the aforementioned 2 : 4-dinitrophenylhydrazone "A", m. p. and mixed m. p. 243° (decomp.), crystallised, and the filtrate when kept overnight deposited a second dinitrophenylhydrazone, m. p. 220—233° (decomp.) depressed to 220—226° by admixture with "A". The residual mother-liquor was now concentrated to half its volume and was seeded with "A". After 2 hours the resulting deposit of slightly impure "A" was filtered off and the filtrate was then seeded with the second dinitrophenylhydrazone, of which a further crop accrued. The combined crops of the second material were crystallised from acetic acid, forming orange-red needles of m. p. 236—238° (decomp.) raised to 238—240° by admixture with the 2 : 4-dinitrophenylhydrazone of (V) (Cook, Dickson, and Loudon, *loc. cit.*) and depressed to 216—224° (decomp.) by admixture with "A".

Cyclisation of (III) *with Hydrogen Fluoride*.—The acid (III) (0·84 g.) was dissolved in hydrogen fluoride (*ca.* 10 c.c.) which was then allowed to evaporate in absence of moisture. The residue, after treatment with cold dilute sodium hydroxide, was recovered in ether and gave 4-phenylindanone (IV), m. p. and mixed m. p. 86—87°, from ethanol (yield 79%). The mother-liquor from the crystallisation gave, on concentration, a yellow gum which when oxidised (cf. above) with sodium dichromate in acetic acid afforded phenanthraquinone, m. p. and mixed m. p. 201—204°, after sublimation; diazine from *o*-phenylenediamine, m. p. and mixed m. p. 216—217°.

Cyclisation of β-(5-Bromo-2 : 3 : 4 : 4′-tetramethoxy-6-diphenylyl)propionic Acid with Hydrogen Fluoride.—The neutral solid (0·38 g.), obtained by treating (I) (1 g.) with hydrogen fluoride as above, was crystallised from petroleum (b. p. 40—60°) and gave, as first crop, warty nodules of the bromo-ketone (II) (0·014 g.), (micro-)m. p. and mixed m. p. 141·5°, which was debrominated to 5 : 6 : 7-trimethoxy-4-*p*-methoxyphenylindan-1-one (cf. Part VIII, *loc. cit.*), (micro-)m. p. and mixed m. p. 84—86°. This compound [oxime, (micro-)m. p. 216°] was also obtained as a second crop of needles from the petroleum mother-liquor of the bromo-ketone.

2 : 3 : 4-Trimethoxydiphenyl-6-carboxylic Acid (IX).—Methyl 3 : 4 : 5-trimethoxybenzoate (265 g.) and 1-phenyl-3 : 3-dimethyltriazen (53 g.) were slowly treated with acetic acid (70 c.c.) at 100° and the whole was heated at 100° for 16 hours. The resulting dark liquid, dissolved in chloroform, was thoroughly washed in turn with dilute hydrochloric acid, water, dilute sodium hydroxide, and again with water, and recovered. Unchanged ester was distilled off up to 185°/10 mm. and the residue was combined with similar residues obtained by renewed interaction of the recovered ester with fresh triazen. In all, 110 g. of the triazen were used in three runs and the crude trimethoxybenzoate finally recovered weighed 200 g. The combined higher-boiling residues on fractional distillation gave: (*a*) a small quantity of unchanged ester, b. p. 180—186°/10 mm.; (*b*) the main, partly solid fraction, b. p. 186—205°/10 mm.; (*c*) an oily fraction, b. p. 204—214°/10 mm. Fractions (*b*) and (*c*) when rubbed each with half its volume of methanol gave solids which were combined (24 g.) and crystallised from methanol (50 c.c.). The resulting crystalline mixture was swirled in the solvent, the lighter material (solid B) was collected by decantation, and the mother-liquor was used for renewed treatment of the heavier constituent. The latter, after further crystallisation from methanol, afforded *methyl 2 : 3 : 4-trimethoxydiphenyl-6-carboxylate* (15 g.), m. p. 71—72° (Found: C, 67·6; H, 5·7. $C_{17}H_{18}O_5$ requires C, 67·5; H, 5·95%), which was hydrolysed by 50% aqueous potassium hydroxide in methanol to the corresponding *acid* (IX), m. p. 196° from methanol (Found: C, 66·95; H, 5·6. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%), and was regenerated from this acid by diazomethane in ether; m. p. and mixed m. p. 71—73°. The combined gums, recovered from the various methanol mother-liquors of the above separation, gave small additional quantities of the products after redistillation and re-treatment, while the final methanol mother-liquors on heating with aqueous alkali gave in addition to some non-saponifiable oil (discarded) a small quantity of the above acid, m. p. 191—193°.

Solid B (2·2 g.) was separated by crystallisation from methanol into a small, sparingly soluble fraction consisting of nacreous platelets, m. p. 210°, probably of *p*-terphenyl (Found: C, 93·6; H, 6·15. Calc. for $C_{18}H_{14}$: C, 93·9; H, 6·1%), and a relatively soluble fraction (1·5 g.) of m. p. 156° (Found: C, 70·6; H, 5·65. $C_{20}H_{16}O_4$ requires C, 70·6; H, 5·9%), which is probably *methyl 2 : 6-dimethoxydiphenyl-4-carboxylate* (cf. Part VIII, *loc. cit.*). The latter compound was hydrolysed by aqueous potassium hydroxide in methanol to the corresponding *acid*, m. p. 237° from methanol (Found: C, 69·8; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

2 : 3 : 4-Trimethoxyfluorenone.—The acid (IX) (0·3 g.) was dissolved and gently warmed (10 minutes) in thionyl chloride. The solvent was distilled off; the residual *ketone* formed long orange needles, m. p. 113°, from methanol (Found: C, 70·8; H, 5·2. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%). It yielded a 2 : 4-*dinitrophenylhydrazone* as fluffy red needles, m. p. 211°, from acetic acid (Found: C, 58·4; H, 3·8. $C_{22}H_{18}O_7N_4$ requires C, 58·7; H, 4·0%).

2 : 3 : 4-*Trimethoxydiphenyl-6-aldehyde* (XI).—**2 : 3 : 4-*Trimethoxydiphenyl-6-carboxyhydrazide***, colourless needles of m. p. 156° from methanol (Found: C, 63·7; H, 5·9. $C_{16}H_{18}O_4N_2$ requires C, 63·8; H, 6·0%), was prepared by heating the methyl ester of (IX) (16·7 g.) and 99% hydrazine hydrate (31 c.c.) in methanol (60 c.c.) for 8 hours. Addition of benzenesulphonyl chloride (9·2 g.) to its solution in cold pyridine (14·1 g. in 84 c.c.), followed after 1 hour by pouring into iced hydrochloric acid, yielded the ***benzenesulphonyl* derivative**, m. p. 162—163° (from methanol) (Found: C, 59·4; H, 4·9. $C_{23}H_{24}O_6N_2S$ requires C, 59·7; H, 5·0%). A solution of the latter (18·5 g.) in ethylene glycol (150 c.c.) at 160° was treated with anhydrous sodium carbonate and, after 100 seconds, the reaction was quenched with boiling water. The required ***aldehyde***, recovered from an alkali-washed ethereal extract, formed almost colourless plates, m. p. 92—93°, from methanol (Found: C, 70·6; H, 5·7. $C_{18}H_{18}O_4$ requires C, 70·6; H, 5·9%).

β-2 : 3 : 4-*Trimethoxy-6-diphenylylacrylic Acid* (XIII).—A solution of the above aldehyde (9·3 g.) and malonic acid (7·4 g.) in dry pyridine (20 c.c.) containing a few drops of piperidine was heated first at 100° (4 hours) and then under reflux (15 minutes). After cooling, pouring into iced hydrochloric acid, and extraction with ether, the required ***acid*** was recovered from aqueous alkali and formed small needles, m. p. 165°, from acetic acid–water (2 : 1) (Found: C, 68·7; H, 5·6. $C_{20}H_{20}O_6$ requires C, 68·8; H, 5·8%).

β-2 : 3 : 4-*Trimethoxy-6-diphenylylpropionic Acid* (XV).—This ***acid*** was prepared by hydrogenating a solution of (XIII) (9·6 g.) in acetic acid (330 c.c.) over palladium-black (0·6 g.). After filtration and recovery the acid formed colourless plates, m. p. 121—122°, from acetic acid–water (1 : 1) (Found: C, 68·7; H, 6·3. $C_{20}H_{22}O_6$ requires C, 68·7; H, 6·3%). Methylation with diazomethane in ether gave the ***methyl*** ester as cubes, m. p. 56°, from light petroleum (b. p. 40—60°) (Found: C, 69·3; H, 6·8. $C_{21}H_{24}O_6$ requires C, 69·1; H, 6·7%).

5 : 6 : 7-*Trimethoxy-4-phenylindan*-1-*one*.—This ***ketone*** was obtained as neutral product in colourless needles of m. p. 74° from petroleum (b. p. 60—80°) (Found: C, 72·9; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%) when the acid (XV; 0·5 g.) was treated with hydrogen fluoride. It formed an ***oxime***, m. p. 200°, from ethanol (Found: C, 68·9, H, 6·0. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1%). Oxidation of the crude product gave no evidence of the formation of a coloured phenanthraquinone derivative.

β-(5-*bromo*-2 : 3 : 4-*trimethoxy-6-diphenylyl)propionic Acid* (VII).—A solution of bromine (0·1 c.c.) in dry chloroform (2·5 c.c.) was added to a solution of (XV) (0·63 g.) in the same solvent (12·5 c.c.) and, after 3 hours at room temperature, the crude product was recovered from the (water-washed) solution. It was purified by conversion into the sparingly soluble sodium salt by concentrated aqueous sodium hydrogen carbonate. The ***bromo-acid*** was regenerated by dilute hydrochloric acid, forming colourless plates, m. p. 164—165°, from acetic acid–water (1 : 1) (Found: C, 54·7; H, 4·8. $C_{20}H_{21}O_6Br$ requires C, 54·7; H, 4·8%) and affording, with diazomethane in ether, the ***methyl* ester**, m. p. 95—96° (from methanol) (Found: C, 55·7; H, 5·0. $C_{21}H_{23}O_6Br$ requires C, 55·6; H, 5·1%).

Attempts to cyclise (VII).—(*a*) The neutral gum obtained from (VII) by treatment with hydrogen fluoride remained resinous after reaction with Girard's reagent-T and hydrolysis of the product. It afforded a bright red **2 : 4**-dinitrophenylhydrazone, but was not converted into a solid by debromination with hydrogen in presence of palladised strontium carbonate. (*b*) The acid (0·7 g.) in dry benzene (10 c.c.) was shaken with phosphorus pentachloride (0·4 g.). Volatile materials were removed under reduced pressure and the residue was treated with carbon disulphide (3 c.c.) and aluminium chloride (0·6 g.). After 2 days at 0° dilute hydrochloric acid was added, the solvent was removed in steam, and the neutral product was recovered from chloroform as a gum. This did not yield a solid on debromination.

Neither of the (debrominated) gums showed any trace of a phenanthraquinone derivative when oxidised with sodium dichromate in acetic acid.

1-*m*-*Methoxyphenyl*-3 : 3-*dimethyltriazen*.—A diazo-solution from *m*-anisidine (100 g.), concentrated hydrochloric acid (200 c.c.), water (200 c.c.), and sodium nitrite (56 g.) was added with stirring to a mixture of 25% dimethylamine (280 g.) and 30% aqueous sodium carbonate (800 c.c.) kept at 0°; the mixture was then stirred for 30 minutes and the product was extracted in benzene and recovered from the dried extract. The ***triazen*** distilled as a yellow liquid (114 g.), b. p. 161°/15 mm. (Found: C, 60·4; H, 6·9. $C_9H_{13}ON_3$ requires C, 60·3; H, 7·25%).

2 : 3 : 4 : 3′-*Tetramethoxydiphenyl-6-carboxylic Acid* (X).—Starting from methyl **3 : 4 : 5**-trimethoxybenzoate (165 g.), the above triazen (32 g.), and acetic acid (43 c.c.) and using in all 125 g. of the triazen in 4 runs as described for (IX), there were obtained recovered initial ester (94 g.) and the following higher-boiling fractions: (*a*) a small fraction, b. p. 185—215°/8 mm.; (*b*) a main fraction, b. p. 203—220°/0·5 mm. On rubbing these combined fractions with half their volume of methanol there was obtained a product, regarded as ***methyl* 2 : 6 : 3′-*trimethoxydiphenyl*-4-*carboxylate*** (cf. Part VIII, *loc. cit.*), m. p. 154—156°, from acetic acid (yield, 2 g.) (Found: C, 67·5; H, 5·7. $C_{17}H_{18}O_5$ requires C, 67·5; H, 5·9%), which was hydrolysed by 50% potassium hydroxide in methanol to the corresponding ***acid***, m. p. 215°, from acetic acid (Found: C, 65·9; H, 5·6. Found, after drying *in vacuo* 100° for 1 hour: C, 66·4; H, 5·2. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·5%), and was regenerated from this acid by diazomethane in ether. The methanol mother-liquor from the foregoing ester contained a second (oily) ester which was hydrolysed to **2 : 3 : 4 : 3′-*tetramethoxydiphenyl-6-carboxylic acid*** (X), colourless prisms, m. p. 134—135° (19 g.), from methanol–water (1 : 1) (Found: C, 64·2; H, 5·8. $C_{17}H_{18}O_6$ requires C, 64·1; H, 5·8%).

2 : 3 : 4 : 6-*and* 2 : 3 : 4 : 8-*Tetramethoxyfluorenone*.—The residue obtained by heating (X) with thionyl chloride and distilling off excess of this reagent crystallised from methanol as a mixture of small lemon-coloured needles (A) and heavier, stout, golden needles (B). These were separated by swirling and decanting (A) with the mother-liquor. ***Fluorenone*-A**, m. p. 122° from methanol (Found: C, 68·1; H, 5·45. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%), afforded a **2 : 4-*dinitrophenylhydrazone*** as fluffy red needles, m. p. 226° from acetic acid (Found: C, 57·6; H, 4·1. $C_{23}H_{20}O_9N_4$ requires C, 57·5; H, 4·2%). ***Fluorenone*-B**, m. p. 152—153° from methanol (Found: C, 68·2; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%), gave a **2 : 4-*dinitrophenylhydrazone***, m. p. 137° depressed by admixture with the isomer (Found: C, 57·8; H, 3·7%).

2 : 3 : 4 : 3′-*Tetramethoxydiphenyl-6-aldehyde* (XII).—This ***compound***, crystallising in colourless

plates, m. p. 60—61°, from methanol (Found : C, 67·4; H, 5·8. $C_{11}H_{14}O_3$ requires C, 67·5; H, 6·0%), and yielding a 2 : 4-*dinitrophenylhydrazone*, m. p. 192° (Found : C, 57·4; H, 4·7. $C_{23}H_{22}O_6N_4$ requires C, 57·3; H, 4·6%), was prepared as described for (XI) *via* the *hydrazide*, m. p. 137—138° (Found : C, 61·6; H, 6·0. $C_{11}H_{16}O_2N_2$ requires C, 61·45; H, 6·0%), and *benzenesulphonhydrazide*, m. p. 182—183°, of the acid (X) (Found : C, 58·5; H, 5·0. $C_{23}H_{24}O_5N_2S$ requires C, 58·7; H, 5·1%). Under the conditions given, decomposition of the sulphonhydrazide was incomplete : the sulphonhydrazide was partly recovered from a chloroform extract of the reaction products by washing with 2*N*-sodium hydroxide, from which it was liberated by saturation with carbon dioxide and on renewed treatment yielded the aldehyde.

β-(2 : 3 : 4 : 3′-*Tetramethoxy*-6-*diphenylyl*)*acrylic Acid* (XIV).—This *acid* which formed colourless needles, m. p. 150—151°, from acetic acid : water (1 : 1) (Found : C, 66·2; H, 5·8. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%), and the corresponding *propionic acid* (XVI), m. p. 90—91° (from dilute acetic acid) (Found : C, 65·7; H, 6·2. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%), were obtained by the methods described for analogous cases.

5 : 6 : 7-*Trimethoxy*-4-*m*-*methoxyphenylindan*-1-*one* was obtained as neutral product from the treatment of the acid (XVI) with hydrogen fluoride. It formed thick colourless plates, m. p. 141—142°, from methanol (Found : C, 69·25; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). An oxidation test on the cyclised material gave no evidence of formation of a phenanthraquinone derivative.

β-(5-*Bromo*-2 : 3 : 4 : 3′-*tetramethoxy*-6-*diphenylyl*)*propionic Acid* (VIII).—The *bromo-acid*, m. p. 163—164° (from acetic acid) (Found : C, 53·8; H, 4·8. $C_{19}H_{21}O_6Br$ requires C, 53·65; H, 5·0%), was prepared from (XVI) as described for the compound (VII).

5 : 6 : 7-*Trimethoxy*-4-(?-*bromo*-*m*-*methoxyphenyl*)*indan*-1-*one*.—Colourless plates, m. p. 115—116° (from methanol) (Found : C, 56·1; H, 4·7. $C_{19}H_{19}O_5Br$ requires C, 56·0; H, 4·7%), of this *ketone* were obtained as neutral product by treating (VIII) with hydrogen fluoride. The gum, recovered from the methanol mother-liquor, did not afford evidence of formation of a phenanthraquinone derivative when oxidised with sodium dichromate in acetic acid.

Debromination. The above bromo-indanone (0·04 g.) in methanol (20 c.c.) was shaken (1 hour) with 2% palladised strontium carbonate in an atmosphere of hydrogen. Concentration of the filtered solution yielded 5 : 6 : 7-trimethoxy-4-*m*-methoxyphenylindan-1-one, m. p. and mixed m. p. 139—141°.

2 : 5-*Dimethoxydiphenyl*-2′-*carboxylic Acid* (XVII).—Glacial acetic acid (60 c.c.) was slowly added to a melt of quinol dimethyl ether (100 g.) and 1-(*o*-carbomethoxyphenyl)-3 : 3-dimethyltriazen (50 g.; cf. Elks and Hey, *J.*, 1943, 443) at 100° and the mixture was maintained at this temperature for 18 hours. The resulting dark liquid was dissolved in chloroform and, after being washed in turn with dilute hydrochloric acid, water, dilute sodium hydroxide and again with water, the solution was dried and concentrated. Distillation of the residue gave the following fractions : (i) quinol dimethyl ether (140 g.), b. p. 110—112°/10 mm.; (ii) a pale yellow oil (3 g.), b. p. 127—132°/10 mm.; (iii) a yellow oil (7 g.), b. p. 196—204°/10 mm., which when rubbed with methanol gave *methyl* 2 : 5-*dimethoxydiphenyl*-2′-*carboxylate*, m. p. 65° from methanol (Found : C, 70·6; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%); (iv) a viscous brownish gum, b. p. 205—215°/10 mm. with much decomposition, yielding a small quantity of unidentified needles, m. p. 291—293°, when rubbed with methanol; (v) a non-volatile residue which was dissolved in chloroform, washed with dilute hydrochloric acid and, combined with the residues from subsequent runs, concentrated, and redistilled, thereby slightly adding to fraction (iv). Fraction (ii), combined with the methanol mother-liquors from fractions (iii) and (iv), gave on hydrolysis (1 hour) with aqueous methanolic potassium hydroxide the *acid* (XVII), m. p. 155° (from methanol), which was also obtained by hydrolysing the pure methyl ester (Found : C, 69·9; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

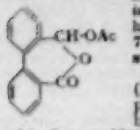
2-*Hydroxy*-5-*methoxydiphenyl*-2′-*carboxylic Acid Lactone* (XVIII).—The preceding acid (0·5 g.) in benzene (5 c.c.) and thionyl chloride (1·2 c.c.) was kept for 12 hours at room temperature. After removal of solvent under reduced pressure (temp. *ca.* 25°), the lactone was obtained as colourless crystals, m. p. 119—120°, from benzene (Found : C, 73·7; H, 4·4; OMe, 13·4. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·4; OMe, 13·7%). It did not give a coloration to aqueous ferric chloride, was insoluble in cold alkali, but dissolved on heating and was regenerated on acidification.

Monobenzenesulphonhydrazide of Diphenic Acid.—(*a*) A suspension of the monohydrazide of diphenic acid (1·3 g.; m. p. with gas evolution 185°; cf. Labriola, *Chem. Zentr.*, 1938, II, 1770) in cold pyridine (4 c.c.) was treated with benzenesulphonyl chloride (0·9 g.) which was washed in with the aid of a further 2 c.c. of pyridine. After 12 hours at room temperature the yellow solution was added to dilute sulphuric acid, yielding the required *product*, m. p. 220° from ethanol–water (Found : C, 60·3; H, 4·1; N, 7·3. $C_{20}H_{16}O_5N_2S$ requires C, 60·6; H, 4·0; N, 7·1%). With acetic anhydride and a trace of sulphuric acid or with acetic anhydride in pyridine it reacted to form an *anhydro-acetyl* derivative, m. p. 216° from acetic acid, which was insoluble in alkali (Found : C, 63·3; H, 3·9; N, 6·5. $C_{22}H_{16}O_6N_2S$ requires C, 62·9; H, 3·8; N, 6·7%).

(*b*) Diphenic anhydride (6·6 g.) was added slowly with cooling to a solution of benzenesulphonhydrazide (5·1 g.) in pyridine (30 c.c.). After 12 hours the solid obtained on pouring into dilute hydrochloric acid yielded the above compound, m. p. and mixed m. p. 220°, from ethanol–water, as main product, while a second product—probably the isomeric *as-diacylhydrazide* [$C_{12}H_8(CO_2H)$·CO·N(NH$_2$)SO$_2$Ph]—m. p. 220° depressed to *ca.* 215° by admixture with the above compound, was obtained in small amount from the mother-liquor (Found : C, 60·6; H, 4·0; N, 6·9. $C_{20}H_{16}O_5N_2S$ requires C, 60·6; H, 4·0; N, 7·1%).

2′-*Formyldiphenyl*-2-*carboxylic Acid* (XIX).—To a solution of the above benzenesulphonhydrazide (2 g.; main fraction) in ethylene glycol (20 c.c.) at 165° anhydrous sodium carbonate (2·5 g.) was added during 30 seconds and after a further 240 seconds the reaction was terminated by cautious addition of boiling water (100 c.c.). After cooling and filtering, unreacted hydrazide was precipitated by a stream of sulphur dioxide, and the resulting mother-liquor, on acidification with dilute sulphuric acid, gave the *acid* (XIX) in 40% yield, m. p. 132° from methanol–water (Found : C, 74·5; H, 4·4. $C_{14}H_{10}O_3$ requires C, 74·4; H, 4·4%).

ω-Acetoxydiphenide (as annexed) was obtained when a solution of (XIX) in acetic anhydride containing a few drops of concentrated sulphuric acid was kept for 12 hours and then poured into water. After recovery from an alkali-washed ethereal extract, the neutral product had m. p. 125° from methanol (Found: C, 71·6; H, 4·3. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). It was reconverted into (XIX) by warming (90 minutes) in dilute sulphuric–acetic acid.



β-(2′-Carboxy-2-diphenylyl)acrylic Acid (XX).—A solution of the aldehydo-acid (XIX) (1·2 g.) and malonic acid (0·55 g.) in pyridine (6 c.c.), containing a few drops of piperidine, was heated first at 100° (1 hour) and then under reflux (15 minutes) before being cooled and poured into dilute hydrochloric acid. The oily product solidified and had m. p. 228° (Rapoport and Williams, *loc. cit.*, record m. p. 230—231° (corr.)], from dilute acetic acid (Found: C, 72·1; H, 4·5. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%). Its titre, determined in methanol solution, showed the compound to be dibasic (Found: equiv., 130. Calc.: equiv., 134).

β-(2′-Carboxy-2-diphenylyl)propionic Acid (XXI).—The above acid, dissolved in acetic acid, was hydrogenated in presence of palladium-black at ordinary temperature and pressure. Hydrogenation was complete in 1½ hours and the product, recovered from the filtered solution, had m. p. 185° from aqueous acetic acid (Found: C, 71·1; H, 4·8. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%). Rapoport and Williams (*loc. cit.*) give m. p. 171—173° (corr.) (prepared by three distinct methods).

Cyclisation of (XXI).—(*a*) The dry barium salt, heated in a sublimation apparatus at 360°/1 mm., yielded an oily sublimate which could not be induced to crystallise but afforded a 2 : 4-dinitrophenylhydrazone, (micro-)m. p. 220° from acetic acid, unchanged by further crystallisation or by admixture with the 2 : 4-dinitrophenylhydrazone of (V), (micro-)m. p. 237°. (*b*) The dry sodium salt (0·11 g.) was heated under reflux with acetic anhydride (2 c.c.) for 1 hour. The solvent was removed under reduced pressure and the residue was treated with dilute alkali and extracted with ether. The oil recovered from the ether yielded a crystalline 2 : 4-dinitrophenylhydrazone, (micro-)m. p. 234° and mixed m. p. 235° with the 2 : 4-dinitrophenylhydrazone of (V).

p-Tolyl 2-o-carboxyphenylthiolbenzoate was prepared by heating (90 minutes) a solution of diphenic anhydride (0·5 g.) and thio-*p*-cresol (0·34 g.) in pyridine at 70°. It solidified when the cooled solution was poured into dilute hydrochloric acid and had m. p. 147° (from methanol–water) (Found: C, 72·8; H, 4·6. $C_{21}H_{16}O_3S$ requires C, 72·4; H, 4·6%). On cooling a solution of the compound in warm dilute sodium hydroxide there was deposited a crystalline product of m. p. 88°, from which the thiol-ester was regenerated by dilute acid and which appeared to be a hydrated *sodium* salt (Found: C, 51·6; H, 5·5. $C_{21}H_{15}O_3SNa,7H_2O$ requires C, 51·6; H, 5·8%).

When treated as in the following case with Raney nickel the half thiol-ester yielded 2′-hydroxymethyldiphenyl-2-carbonylic acid, m. p. 145—146° [from ether–light petroleum (b. p. 40—60°)], which was converted by heating at 110° for 1 hour into diphenide, m. p. and mixed m. p. 132° (Kenner and Turner, *J.*, 1911, **99**, 2101, give m. p.s 146° and 132°, respectively).

p-Tolyl o-Carbomethoxythiolbenzoate.—A solution of equivalent amounts of *o*-carbomethoxybenzoyl chloride and thio-*p*-cresol in cold pyridine was poured, after 12 hours, into iced dilute hydrochloric acid. The product, washed with alkali, dried, recovered in ether, and crystallised from methanol, had m. p. 58—59° (Found: C, 67·3; H, 4·9. $C_{16}H_{14}O_3S$ requires C, 67·1; H, 4·9%). A solution of this compound (1·5 g.) in 70% ethanol (30 c.c.) was heated under reflux with suspended Raney nickel (7·5 g.) for 90 minutes. After filtration, concentration, and an ineffective attempt to separate aldehydic material by means of sodium hydrogen sulphite solution, the resulting oil slowly solidified, giving crystals of m. p. and mixed m. p. with phthalide 71—72°.

p-Tolyl thiolbenzoate (2 g.) in 70% ethanol (40 c.c.) with Raney nickel (10 g.) in suspension was heated under reflux for 6 hours. On distillation from a water-bath the ethanol entrained some benzaldehyde, isolated as 2 : 4-dinitrophenylhydrazone (0·25 g.), m. p. and mixed m. p. 235°, whilst the residue afforded benzyl alcohol (0·25 g.), b. p. 178°/24 mm., characterised as the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 110—112°.

Ethyl thiolbenzoate (9·5 g.) in 70% ethanol (180 c.c.) was heated under reflux with Raney nickel (54 g.) for 2 hours. The filtrate from the nickel was diluted with water and extracted with ether. The ether was removed through an efficient reflux column and the residue was cautiously treated with an excess of concentrated nitric acid, nitration being completed by heating under reflux for 1 hour. Nitrobenzene was isolated by distillation, b. p. 208—210°, and was identified by conversion (Raney nickel and hydrogen) into aniline, b. p. 180—182°, and thence into acetanilide and tribromoaniline. The yield of benzene, based on the aniline found, was 60%.

p-Tolyl 3 : 4 : 5-*Trimethoxythiolbenzoate*.—Thio-*p*-cresol (2·6 g.) in dry pyridine (14 c.c.) was treated with finely powdered 3 : 4 : 5-trimethoxybenzoyl chloride and the whole was heated at 80° for 1 hour. The cooled mixture was poured into iced hydrochloric acid and, after recovery in benzene, the *thiol*-ester formed colourless plates, m. p. 102° (Found: C, 64·2; H, 5·4. $C_{17}H_{18}O_4S$ requires C, 64·35; H, 5·4%).

Reaction with Raney Nickel.—(i) The thiol-ester (2·25 g.) in 70% ethanol (50 c.c.) containing Raney nickel (12 g.) in suspension was heated under reflux for 6 hours. After recovery and distillation there were obtained: (i) 1 : 2 : 3-trimethoxybenzene (0·24 g.), b. p. 80° (0·5 mm., m. p. 42—43° from petroleum (b. p. 40—60°), forming a *picrate*, golden needles of m. p. and mixed m. p. 79—80° (Found: C, 45·8; H, 3·8; N, 10·4. $C_{15}H_{15}O_{10}N_3$ requires C, 45·4; H, 3·8; N, 10·6%), and further characterised by oxidation with dilute nitric acid to 2 : 6-dimethoxybenzoquinone, m. p. 246—248°; (ii) 3 : 4 : 5-trimethoxybenzyl alcohol (0·62 g.), b. p. 152—154°/0·5 mm., identified as the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 147—148° (Cook, Graham, and Cohen, *J.*, 1944, 323) (Found: C, 52·3; H, 4·15. Calc. for $C_{17}H_{16}O_9N_2$: C, 52·1; H, 4·1%).

(ii) The thiol-ester (4 g.) in dioxan (40 c.c.) was treated with a suspension of Raney nickel (32 g.) in dioxan (40 c.c.). Heat was evolved and the reaction was completed by shaking for 1 hour at room temperature. 1 : 2 : 3-Trimethoxybenzene (0·705 g.) and 3 : 4 : 5-trimethoxybenzyl alcohol (1·05 g.) were again isolated as under (*a*).

Ethyl 3 : 4 : 5-*trimethoxythiolbenzoate* (7 g.), b. p. 185°/0·3 mm., m. p. 35—36° from light petroleum

(b. p. 40—60°) (Found : C, 56·3; H, 6·3. $C_{11}H_{14}O_4S$ requires C, 56·3; H, 6·25%), treated as in experiment (i), gave 1 : 2 : 3-trimethoxybenzene (1·1 g.) and 2 : 4 : 5-trimethoxybenzyl alcohol (2·1 g.).

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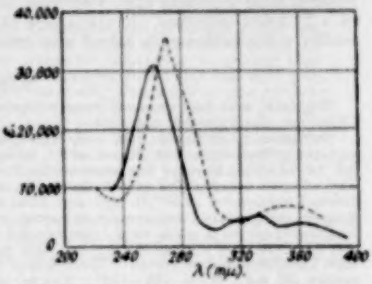
31. *The Structure of Stipitatic Acid.*

By R. E. CORBETT, A. W. JOHNSON, and A. R. TODD.

Oxidation of stipitatic acid with alkaline hydrogen peroxide gives a mixture of aconitic and malonic acid, indicating that stipitatic acid is 6(4)-hydroxytropolone-4(6)-carboxylic acid (I or II).

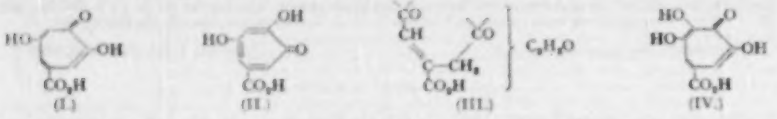
STIPITATIC ACID, $C_9H_8O_6$, was isolated from the culture media of *Penicillium stipitatum* Thom by Birkinshaw, Chambers, and Raistrick (*Biochem. J.*, 1942, **36**, 242), who carried out a number of degradative experiments but were unable to advance a satisfactory structural formula. The compound was optically inactive, contained no *C*-methyl groups but had three active hydrogen atoms, and it titrated as a dibasic acid. On acetylation, two isomeric diacetyl derivatives were obtained, both soluble in sodium carbonate solution, and on methylation two isomeric trimethyl derivatives were formed, both neutral and insoluble in cold dilute aqueous sodium hydroxide. Other derivatives of stipitatic acid which were described included a dimethyl compound, soluble in dilute sodium hydroxide but insoluble in sodium hydrogen carbonate, formed from it by the action of hot methanolic hydrogen chloride or from disodium stipitatate by methyl iodide; a dibasic monomethyl derivative obtained by treatment of the acid with methyl sulphate in the presence of methanolic potassium hydroxide; and finally a monobromo-substitution product prepared by bromination in aqueous acetic acid. This bromo-derivative titrated as a dibasic acid and gave a neutral compound, "bromotrimethylstipitatic acid," on methylation with diazomethane. These facts indicated the presence of two enolic (or phenolic) groupings of varying acid strengths and one carboxyl group, whose presence was confirmed by decarboxylation of stipitatic acid to give a compound, $C_7H_8O_4$, which was monobasic and gave a blood-red precipitate with ferric chloride. Although no evidence was obtained for the presence of a free carbonyl group, hydrogenation in the presence of platinum, or reduction with zinc and acetic acid, gave products which gave positive carbonyl reactions, and this suggested the presence of a masked carbonyl group in stipitatic acid. The five oxygen atoms were thus accounted for in two enolic hydroxyl groups, one carboxyl and one masked carbonyl group. The titratable acidity of reduced stipitatic acid was one-half that of the original acid, presumably owing to the reduction of the acidic enolic group. A most important observation was made on fusing stipitatic acid or its monomethyl derivative with potassium hydroxide at 300°, when 5-hydroxy*iso*phthalic acid was obtained in good yield. No satisfactory structure was advanced to explain all of these findings and, in particular, a dihydroxyformylbenzoic acid structure was shown to be untenable. The similarity in the general behaviour of stipitatic acid and puberulic acid, noted by Raistrick and his colleagues, is further emphasised by the similarity of their ultra-violet absorption spectra (see figure).



Ultra-violet absorption spectra of puberulic (·····) and stipitatic acid (——) in aqueous solutions.

In 1945, Dewar (*Nature*, **155**, 50) re-examined the above evidence and suggested that stipitatic acid was probably the hydroxytropolonecarboxylic acid (I), or the tautomeric form (II), although no further experimental evidence was provided. Nevertheless, Dewar showed that such a structure would offer a satisfactory explanation of the various reactions described by Birkinshaw, Chambers, and Raistrick (*loc. cit.*). Thus the isomeric trimethyl compounds are derived from (I) and (II) and the dimethyl derivative is probably methylated on the

carboxyl and ketol groups, the acidity being due to the remaining enolic grouping. The formation of 5-hydroxy*iso*phthalic acid was ascribed to a benzilic acid type of rearrangement



of the tropolone ring and this view is supported by more recent work on tropolone derivatives (*e.g.*, Barltrop and Nicholson, *J.*, 1948, 116; Erdtman and Gripenberg, *Acta Chem. Scand.*, 1948, **2**, 625; Cook and Somerville, *Nature*, 1949, **163**, 410).

We have now obtained degradative proof that structure (I) correctly represents stipitatic acid, for oxidation with alkaline hydrogen peroxide at room temperature gives a mixture of aconitic and malonic acid. The isolation of aconitic acid indicates that stipitatic acid can be represented by (III), and as a benzenoid structure has been shown to be untenable, the only feasible structure for the molecule is (I) or the tautomer (II). Since it has been shown (Corbett, Johnson, and Todd, *J.*, 1950, 6) that puberulic acid is represented by (IV) or one of its tautomeric forms, this acid can be regarded as a hydroxy-stipitatic acid; that this might prove to be the case was originally suggested by Dewar (*Nature*, 1945, **155**, 479).

Further evidence in favour of structure (I) is obtained by the periodate oxidation of hydrogenated stipitatic acid, 0·85 mole of reagent being consumed, indicating the presence of a 1 : 2-diol structure; in the course of this experiment we confirmed that the titratable acidity of stipitatic acid is halved after reduction.

Experimental.

Stipitatic acid was prepared from cultures of *P. stipitatum* Thom as described by Birkinshaw, Chambers, and Raistrick (*loc. cit.*).

Oxidation of Stipitatic Acid with Hydrogen Peroxide.—Stipitatic acid (1·5 g.) was dissolved in aqueous sodium hydroxide (30 c.c. of N.), hydrogen peroxide (14 c.c. of 31%) added, and the mixture left for 72 hours at room temperature, the solution changing from orange-red to pale golden-yellow. This solution was acidified with hydrochloric acid (32 c.c. of N.) (evolution of carbon dioxide), and the mixture evaporated at 50°/13 mm. and dried *in vacuo* over phosphoric oxide. The colourless, rather gummy residue was continuously extracted with dry ether for 9 hours, and the extract was then evaporated giving a white solid contaminated with some colourless resin (100 mg.). The white solid was dissolved in dry ether (5 c.c.), and light petroleum (b. p. 40—60°) was added at the b. p. until a faint cloudiness was produced. The solution, set aside at 0° for 24 hours, deposited small colourless prisms (30 mg.), m. p. 186—187°. The m. p. was not raised by recrystallisation from ether–light petroleum and was unchanged on admixture with authentic aconitic acid (m. p. 186—187°) (Found: C, 41·6; H, 3·6. Calc. for $C_6H_6O_6$: C, 41·4; H, 3·5%).

Under the conditions of the fluorescein reaction, the oxidation product gave, with resorcinol–sulphuric acid, a red solution with a pale greenish-yellow fluorescence in daylight, and a beautiful sky-blue fluorescence in ultra-violet light, identical with that observed using authentic aconitic acid. With pyridine and acetic anhydride it showed the same series of colour changes as authentic aconitic acid.

The mother-liquors, after removal of the aconitic acid, were again brought to the b. p. and a further quantity of light petroleum added to induce further crystallisation. The solution was set aside at 0° for 24 hours, and a further crop of somewhat less pure aconitic acid (20 mg.), m. p. 160—165°, collected. The mother-liquors were evaporated to dryness, and the white residue (50 mg.) sublimed at 80—85°/10^{-4} mm. giving a colourless micro-crystalline sublimate (21 mg.), m. p. 120—125°, and leaving behind a residue of slightly impure aconitic acid, m. p. 178—179°. The sublimate was purified by resublimation at 80°/10^{-4} mm. and formed small colourless prisms, m. p. 131—133°, which had m. p. 134—135° when mixed with malonic acid (m. p. 135—136°) (Found: C, 34·7; H, 4·4. Calc. for $C_3H_4O_4$: C, 34·6; H, 3·8%). The identity of this product with malonic acid was confirmed by the identity of their colour changes with acetic anhydride and by treatment with resorcinol–sulphuric acid under the conditions of the fluorescein reaction, both giving orange-red solutions with a yellow fluorescence in daylight and a pale greenish-blue fluorescence in ultra-violet light.

Periodate Oxidation of Reduced Stipitatic Acid.—Stipitatic acid (616 mg.) was dissolved in dry methanol (75 c.c.) and hydrogenated at atmospheric pressure using Adams's platinum catalyst, 4·6 moles of hydrogen being absorbed. Aliquots of the methanolic solution, titrated before and after reduction, required 13·3 c.c. and 6·37 c.c. of N/100-alkali, respectively. Removal of the methanol under reduced pressure left a colourless gum, which was exactly neutralised with N-sodium hydroxide and extracted continuously with ether for 9 hours. Evaporation of the ethereal extract yielded only a trace of a neutral gum which gave no reaction with Brady's reagent. Reduced stipitatic acid was regenerated from its sodium salt by passage through a pre-treated resin column and, after removal of the water by evaporation under reduced pressure, was obtained as a colourless gum (376 mg.). A solution of this reduced stipitatic acid in water was oxidised with sodium periodate; it consumed 0·85 mole of oxidising agent.

Light Absorption.—An aqueous solution of puberalic acid showed maxima at 2700 and 3500 A.; $\varepsilon_{max.}$ 35,200 and 7160. An aqueous solution of stipitatic acid showed maxima at 2620, 3320, and 3600 A.; $\varepsilon_{max.}$ 30,800, 5150, and 4050 respectively.

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32. *The Deamination of Amino-acids by Nitrous Acid with Particular Reference to Glycine. The Chemistry underlying the Van Slyke Determination of α-Amino-acids.*

By A. T. AUSTIN.

The deamination of α-amino-acids by nitrous acid, which is the basis of the Van Slyke gasometric method for the determination of amino-acids, is not, as is generally considered, accurately described (for the example of glycine) by the equation :

$$H_3N^+{\cdot}CH_2{\cdot}CO_2^- + HNO_2 \longrightarrow HO{\cdot}CH_2{\cdot}CO_2H + N_2 + H_2O$$

In the case of glycine the gas evolved is a mixture of nitrogen, carbon dioxide, and nitrous oxide, and increases in volume with increasing nitrite-ion concentration. There is a corresponding decrease in the amount of glycollic acid in the reaction residue, and from this residue nitromethane and methyl nitrolic acid have been isolated. These facts are explained by the assumption that in the deamination process an intermediate is formed which can interact with negative ions, such as chloride or nitrite ions (giving α-substituted acids), or with water molecules (giving α-hydroxy-acids). By nitrite-ion interaction it appears that α-nitroacetic acid is formed in the above reaction, and it has been shown that this acid may either decompose to nitromethane and carbon dioxide or react with nitrous acid to give methylnitrolic acid and carbon dioxide. At pH 4—5 methylnitrolic acid is converted into a polymer of fulminic acid with much frothing. This polymer breaks down to formohydroxamic acid, and it is shown that, under the above experimental conditions, 10% of this decomposes to cyanic acid and 90% to formic acid and hydroxylamine. The latter with nitrous acid gives nitrous oxide. An explanation is thus obtained for the anomalous gas volumes and troublesome frothing encountered in the Van Slyke nitrous acid determination of glycine.

THE analytical determination of aliphatic amino-groups by the reaction with nitrous acid and measurement of the volume of nitrogen liberated presents an anomaly with α-amino-acids : this is that the volume of gas obtained is greater, in varying degree, than is indicated by the equation :

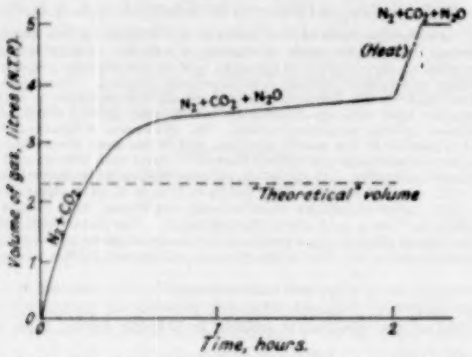
$$H_3N^+{\cdot}CHR{\cdot}CO_2^- + HNO_2 \longrightarrow HO{\cdot}CHR{\cdot}CO_2H + N_2 + H_2O \quad . \quad . \quad . \quad . \quad (1)$$

It was in connexion with α-amino-acids that the special advantages of the procedure developed by Van Slyke (*J. Biol. Chem.*, **1911**, **9**, 185; **1912**, **12**, 275; **1929**, **83**, 425) were most useful; but the uncertainty arising from the fact that "too much" nitrogen was evolved, together with a considerable amount of carbon dioxide, and that extensive frothing often occurred, made it apparent that the reaction was not adequately described by equation (1). Several of the amino-acids that gave anomalous gas volumes contained other NH_2-groups (amido) or peptide linkages (that could react after splitting); and, in the absence of analytical determination of the products, it was impossible to say that the excess of gas did not arise from this source. However, this uncertainty does not exist with glycine (and other monoamino-acids all the nitrogen in which is evolved), so that the excess of gas must have its origin connected in some way with the nitrite ion or nitrous acid. Van Slyke was of the opinion that the diazo-intermediate postulated could decompose in two ways, to give either the hydroxy-compound or, by total disruption of the molecule, carbon dioxide and "some other gas." Later investigators (Schmidt, *J. Biol. Chem.*, **1929**, **82**, 587; Lough and Lewis, *ibid.*, **1934**, **104**, 601; Kendrick and Hanke, *ibid.*, **1937**, **117**, 161; **1940**, **132**, 739; Viscontini, *Helv. Chim. Acta*, **1946**, **29**, 1491) considered that oxidation by the nitrous acid was the source of the carbon dioxide, the nitrous acid being reduced to nitrogen. It has been suggested by others that nitrous acid de-amination may be a more complex reaction than is indicated by equation (1), and Treves and Salomone (*Biochem. Z.*, **1908**, **7**, 11) and Dunn and Lewis (*J. Biol. Chem.*, **1921**, **49**, 327) observed the red colour of the alkaline solution after the deaminising of certain proteins. In the absence of further data they were unable to suggest the nature of these secondary reactions. The present paper is confined to the general chemistry of the reaction of nitrous acid with

glycine, and forms part of an investigation dealing with the mechanism and products of nitrous acid–amine reactions.

A clue to the more detailed behaviour of the nitrous acid reaction with α-amino-acids was obtained during a study of the reaction of methylamine with nitrous acid (to be published later). It was found that an appreciable amount of nitromethane could be isolated. It was postulated, by analogy, that under similar conditions the corresponding α-nitro-carboxylic acid may be formed in reaction (1); and it is well known that such compounds are readily decarboxylated to yield nitroparaffins. Moreover, such α-nitro-acids would be expected to be very reactive to nitrous acid, and it seemed plausible that this was the cause underlying the anomalous behaviour of the α-amino-acids and, in particular, the source of the carbon dioxide. Although the present investigation has been confined to the first member of the series, glycine, considerable support was given to the above postulate when it was found that the greater the nitrite-ion concentration in the reacting solution the greater was the excess of evolved gas over the amount predicted by equation (1). Furthermore, the reaction residue became red when made alkaline; this colour could be discharged on acidification, and ether-extraction from the acid solution yielded pale yellow needles of methyl nitrolic acid.

FIG. 1.



Evolution of gas from glycine (0·1 mole) + sodium nitrite (0·6 mole) in water (300 ml.) when slowly acidified at 10° and then heated.

The reaction was carried out by slow addition of acid to the glycine solution containing the appropriate amount of sodium nitrite. The nature of the gas evolution is shown in Fig. 1. A rapid evolution of gas consisting of nitrogen (~75%) and carbon dioxide (~25%) was followed by a slow, but steady, evolution of a mixture of nitrogen, carbon dioxide, and *nitrous oxide*, together with nitric oxide from decomposition of the nitrous acid. This slow secondary gas evolution was observed by Levene and Van Slyke (*J. Biol. Chem.*, 1912, **12**, 285) and Schmidt (*loc. cit.*), although its nature was not investigated. Initially the reaction solution is almost colourless, but, on the addition of acid, it quickly develops a reddish-brown colour, which soon becomes green. In order to accelerate the slow gas evolution the reaction products were heated after 2—3 hours. When heated, the solution became very dark green, and much gas was evolved. The solution then suddenly became paler—to a reddish-orange, and finally to a very pale yellow—and the gas evolution ceased. The final volume of gas obtained is shown by the broken line in Fig. 1. A pronounced odour of hydrogen cyanide was always observed after this final heating.

With greater concentrations of sodium nitrite the phenomena were essentially the same, but the volume of gas obtained was considerably increased, particularly that of carbon dioxide. These results are shown in Table I.

Considerable frothing occurred during reaction at the two higher nitrite concentrations and it was with some difficulty that this was controlled at the highest concentration. This moderately stable froth, which tends to cause the reaction contents to pass over into the gas-collecting apparatus, is discussed below.

TABLE I.

Gas evolution (N.T.P.) *when* 50 *ml. of hydrochloric acid* (2·0*N*.) *are slowly added to glycine* (0·1 *mole*) *and sodium nitrite* (*x mole*) *in* 300 *ml. of water. Theoretical volume according to equation* (1), 2·24 *l.*

Amount of glycine, mole.	Initial amount of $NaNO_2 = x$, mole.	N_2, l.	CO_2, l.	N_2O, l.	$\frac{N_2 \text{ (expt.)}}{N_2 \text{ (theor.)}}$	$\frac{\text{[Nitrite]}}{\text{[Glycine]}}$
0·100	0·300	2·45	0·69	0·32	1·09	3
0·100	0·600	2·68	0·97	0·37	1·19	6
0·100	1·200	2·72	1·13	0·45	1·23	12

The amount of glycollic acid in the residues showed a progressive decrease, corresponding to the anomalous results described above; these results are contained in Table V.

When the reaction between glycine and nitrous acid was carried out in the cold with very slow generation of nitrous acid it was possible to isolate nitromethane by distillation and fractionation of the residue. If, however, the acid was added at all rapidly, nitromethane could not be isolated and ether-extraction of an unheated portion of the solution yielded pale yellow crystals of methylnitrolic acid (together with a yellow oil—see below). This behaviour was consistent with that of nitroacetic acid, as was directly shown by experiment. The successful isolation of the products of the self-decomposition of nitroacetic acid on the one hand, and also of the products of its reaction with nitrous acid on the other, confirms beyond reasonable doubt its formation in the above reaction. It has not, however, been possible to isolate nitroacetic acid from the reaction mixture, for the above reasons, and in order to check the hypothesis further and at the same time obtain an estimate of the amount of nitro-acid formed, the empirical method was adopted of running a solution of synthetically prepared nitroacetic acid into a solution of sodium nitrite which was being slowly acidified. In this way one would be imitating the abnormality postulated in the glycine reaction, and one would look for all the abnormal behaviour observed in this reaction, *viz.*, (1) excessive yield of nitrogen, (2) the formation of carbon dioxide and nitrous oxide, (3) the striking colour changes: colourless ⟶ reddish-brown ⟶ dark green, and, on heating, very dark green ⟶ reddish-orange ⟶ pale yellow, (4) the extensive frothing, (5) the strong odour of hydrocyanic acid on distillation and fraction of the reaction residues. The duplication of behaviour was exact. Table II shows the quantities of gas evolved when potassium nitroacetate reacts with nitrous acid and the resultant solution is heated.

TABLE II.

Potassium nitroacetate, g.	N_2, l.	CO_2, l.	N_2O, l.
4·00	0·22	0·58	0·26
6·00	0·26	0·80	0·30

Cf. the result of the reaction of glycine (0·1 mole) and sodium nitrite (0·3 mole):

0·21 * 0·60 0·32

* Excess of nitrogen, unaccounted for on basis of equation (1).

This reaction of the nitroacetate ion with nitrous acid may be formulated as follows:

$$O_2N{\cdot}CH_2{\cdot}CO_2H + HNO_2 \longrightarrow [O_2N{\cdot}C(:N{\cdot}OH){\cdot}CO_2H] \longrightarrow O_2N{\cdot}CH{:}N{\cdot}OH + CO_2 \quad . \quad (2)$$

The intermediate oximino-compound is immediately decarboxylated to give methylnitrolic acid, which then gives rise to nitrogen, carbon dioxide, and nitrous oxide, as shown below. The initial reaction in equation (2) probably involves the *aci*-form of the nitroacetate ion, as appears to be the case with other similar nitrosations, *e.g.*, the reaction of nitromethane with nitrous acid. When the reaction with nitroacetic acid was carried out at 0°, carbon dioxide was quantitatively evolved in accordance with equation (2), and ether-extraction of the solution yielded crystals of methylnitrolic acid together with the yellow oil—again in agreement with the behaviour with glycine. This oil is being further investigated; but it is thought to be dinitromethane, obtained from the oxidation of the methylnitrolic acid.

A reaction similar to that represented by equation (2) was observed by Ponzio (*Gazzetta*, 1903, **33**, I, 510). The action of dinitrogen tetroxide dissolved in ether on oximinoacetic acid caused decarboxylation, to give methylnitrolic acid. It would seem that the unstable intermediate postulated above is formed in this reaction too:

$$HO{\cdot}N{:}CH{\cdot}CO_2H \xrightarrow{N_2O_4} [HO{\cdot}N{:}C(NO_2){\cdot}CO_2H] \longrightarrow HO{\cdot}N{:}CH{\cdot}NO_2 + CO_2$$

Jovitschitsch (*Ber.*, 1905, **28**, 1213) isolated the ester of this unstable intermediate by the action of nitric acid (*d* 1·2) on ethyl oximinoacetoacetate.

Attention was next directed to the reactions of methylnitrolic acid, in order to determine the contributions of this substance to the reactions. In alkaline solution it has a red colour, which is destroyed on acidification. Wieland (*Ber.*, 1907, **40**, 418) has shown that this acid decomposes into fulminic acid and nitrous acid, and suggested the intermediate formation of the unstable isomeric nitrile oxide, $H{-}C{\equiv}N{\rightarrow}O$. By slow addition of alkali to an ice-cold solution of methylnitrolic acid he obtained a white precipitate which he formulated as a cyclic polymer of this isomer of fulminic acid and called trifulmin (*ibid.*, 1909, **42**, 808). If, however, the alkali is added to the solution at room temperature (20—25°) very extensive frothing occurs, and this has been shown to take place at pH 4—5. The above solutions of glycine and sodium nitrite, and of potassium nitroacetate and sodium nitrite are buffered approximately to this pH, and it is thus easy to understand the frothing. Wieland showed that in acid solution trifulmin was converted into formic acid and hydroxylamine hydrochloride, and, in alkaline solution, into cyanic acid; and he postulated the intermediate formation of formohydroxamic acid, HO·CH:N·OH, which he detected by colour tests with ferric ions (cherry-red) and cupric ions (green). Table III shows the quantities of gas evolved when a solution of synthetically prepared methylnitrolic acid was run into a solution of sodium nitrite that was being slowly acidified. The froth formed was vigorously stirred into solution. The striking colour changes noted above were again observed, and also the odour of hydrocyanic acid after the heating of the solution.

TABLE III.

Methylnitrolic acid, g.	N_2, l.	CO_2, l.	N_2O, l.
1·40	0·17	0·20	0·17
3·38	0·40	0·39	0·44

The dual mode of decomposition of formohydroxamic acid led to similar experiments being carried out on synthetically prepared acid, in order to determine the relative proportions of the two modes under the experimental conditions used, and also to ascertain the fate of the decomposition products in the nitrous acid solution. This decomposition of formohydroxamic acid may be represented:

$$NH_3 + CO_2 \longleftarrow HNCO \longleftarrow HO{\cdot}CH{:}N{\cdot}OH \longrightarrow H{\cdot}CO_2H + NH_4{\cdot}OH$$

The data in Table IV show the quantities of gas obtained when a solution of formohydroxamic acid is heated with an acid sodium nitrite solution (as in the experiments with glycine, with potassium nitroacetate, and with methylnitrolic acid).

TABLE IV.

Formhydroxamic acid, g.	N_2, l.	CO_2, l	N_2O, l.
1·53	0·26	0·04	0·34

As expected, the cyanic acid formed in the reaction immediately decomposes to carbon dioxide and ammonia, the latter with nitrous acid then giving nitrogen. By a similar reaction part of the hydroxylamine gives nitrous oxide, and part decomposes to nitrogen and ammonia (which with nitrous acid gives nitrogen). The formic acid remains unchanged and may be detected by its reducing properties.

Most of the carbon dioxide obtained in the glycine reactions comes, therefore, from the decarboxylation of the nitrosated nitroacetic acid, and estimates were made on this basis, with the help of the data of Table II, of the amounts of nitro-acid formed in the different glycine–sodium nitrite solutions. These amounts are shown in Table V (col. **3**), and compared with the analytical determinations of glycollic acid in the residues (col. **4**).

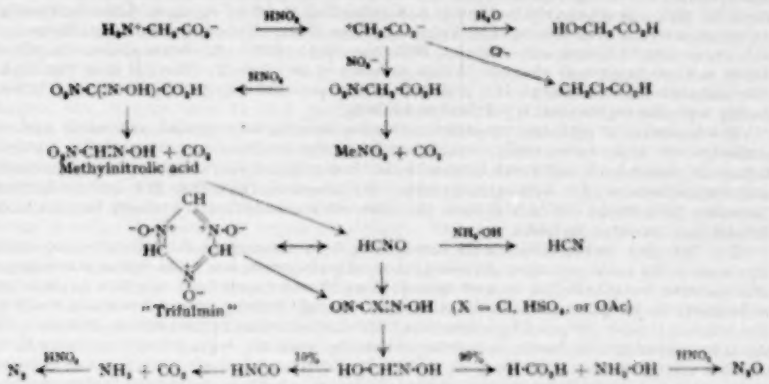
TABLE V.

Glycine, mole.	Initial, $NaNO_2$, mole.	Nitroacetic acid, mole.	Glycollic acid, mole.
0·100	0·300	0·03	0·055
0·100	0·600	0·04	0·039
0·100	1·200	0·05	0·032

The accumulated evidence now permits co-ordination of the behaviour observed when glycine reacts with nitrous acid in the presence of nitrite ion. The sequence of reactions may be formulated as shown in the reaction chart.

The detailed mechanism of the process involved in the removal of the NH_2-group has yet to be confirmed, but steps leading to a carbonium ion are postulated, and glycollic acid would be formed by interaction of this ion with water molecules. The carbonium ion may also react with negative ions in solution to give nitroacetic acid (which then undergoes the series of changes represented) or chloroacetic acid (which has been isolated), by interaction with nitrite and chloride ions, respectively. It would be expected that the greater the ionic concentration the greater would be the amount of substituted acid formed and, as shown in Table I, this has been found in the case of solutions containing varying amounts of nitrite ion.

In the reaction scheme the nitroacetic acid is represented as reacting with nitrous acid with *subsequent* decarboxylation, and not as undergoing preliminary decarboxylation followed by reaction of the nitromethane with the nitrous acid to give methylnitrolic acid. The reason



is that decarboxylation of nitroacetic acid is comparatively slow at 0° (and even at 20°), whereas in the presence of nitrous acid the carbon dioxide is liberated immediately. The nature of this reaction, which is used as a test for nitroacetic acid, does not appear to have been previously considered in detail.

The reaction solutions always developed a green colour, which was more intense the lower the temperature and the higher the nitrite-ion concentration. It was at first thought that methylnitrosolic acid ($ON{\cdot}CH{:}NOH$, from HONC and HNO_2) was the cause of the colour. This acid is known to be green and to decompose to formohydroxamic acid (Wieland and Hess, *Ber.*, 1909, **42**, 4175). However, methylnitrosolic acid is easily extracted by ether (to give a green extract), whereas the green colour in the glycine, nitroacetic acid, and methylnitrolic acid reaction solutions could not be removed in this way. Therefore, it appeared that the colour might be that of the anion of a more acidic nitroso-compound. The moderately stable green colour was obtained irrespective of the acid used (hydrochloric, sulphuric, acetic). When, however, hydrochloric acid was added in excess of that required for reaction the green colour became deep blue. This colour could easily be extracted by ether. On drying of the ethereal extract the colour changed to emerald-green. Evaporation of the ether under reduced pressure yielded a green oil, which was explosive at room temperature, and from its reactions was considered to be a chloronitroso-compound. Its constitution has yet to be confirmed. The green oil becomes blue when added to water, and, on addition of alkali, olive-green. These colour changes are reversible. This suggested that the green colour of the reaction solution might be caused by the ion of the chloronitroso-compound, $ON{\cdot}CCl{:}NO^-$ (which would be stabilised by resonance). With sulphuric and with acetic acid the anions formed would be $ON{\cdot}C(HSO_4){:}NO^-$ and $ON{\cdot}C(OAc){:}NO^-$, respectively. It is assumed that in these cases the free (un-ionised) acids are too unstable to exist in visible concentration. [Nef found that $CHCl{:}N{\cdot}OH$ is much more stable than $CH(HSO_4){:}N{\cdot}OH$; *Annalen*, 1894, **280**, 316.] The blue colour of the aqueous reaction solutions and the behaviour

of the green oil were observed whenever hydrochloric acid was used in the treatment of glycine, nitroacetic acid, or methylnitrolic acid with nitrous acid. The gas evolutions were, however, independent of the acid employed.

The white solid obtained by Wieland (*loc. cit.*) on addition of alkali to methylnitrolic acid is very explosive when dry, and is insoluble in all ordinary solvents. Wieland considered it to be a trimer of an isomer of fulminic acid, and assigned to it a cyclic structure by analogy with the structures accepted at that time for cyanuric acid and cyamelide. In the light of present knowledge it seems that the properties of this substance would be more consistent with a straight-chain indefinite polymer $[{>}CH{\cdot}N^{+}{\cdot}(O^{-})^{+}]_n$. The froth obtained in the experiments with glycine (cf. p. 150) appeared to be gas, from decomposition of part of the solid, enclosed in liquid films stabilised by the unchanged dispersed solid. As such it was difficult to suck dry on the filter funnel but, when dry, it had the same explosive properties as the more easily filtered substance obtained at 0° from methylnitrolic acid. One of the difficulties encountered in the Van Slyke determination of amino-acids by nitrous acid is the extensive frothing that often occurs, which tends to carry the reactants into the gas-measuring compartments. The cause of this was previously unknown, and octan-2-ol is added in these determinations in an attempt to diminish this trouble (Peters and Van Slyke, "Quantitative Clinical Methods," Vol. II, p. 385, Williams and Williams, Baltimore, Md., 1932). As shown above, the pH at which methylnitrolic acid changes to this polymer is about 4—5. The pH in a Van Slyke determination is in this range, and it is thus easy to see that any methylnitrolic acid formed during a glycine determination will lead to frothing.

The formation of hydrogen cyanide in all cases, starting from glycine, nitroacetic acid, or methylnitrolic acid, undoubtedly owes its origin to the oxidising properties of the unstable isomer of fulminic acid, and is correlated with the observation of Wieland (*loc. cit.*) that trifulmin and hydroxylamine gave hydrogen cyanide. Nef (*Annalen*, 1894, **280**, 330) and Schischkoff (*Annalen*, 1861, Suppl. Vol. **1**, 108) have also observed the formation of hydrogen cyanide from fulminic acid in reducing media.

It is clear that ion interaction is the determining factor causing the deviations from equation (1); and, in the usual procedure the anion involved is the nitrite ion. The subsequent changes that the nitroacetic acid thus formed may undergo allow an essentially complete explanation to be drawn up for the manifold series of changes observed in the glycine–nitrous acid reaction. The reaction is more disturbed by interaction with nitrite ion than by that with chloride ion; for the latter, forming chloroacetic acid, may eventually yield the expected hydroxy-compound, whereas the nitroacetic acid, being so reactive to nitrous acid, results in extensive changes. Although it has generally been asserted that oxidation was the source of the carbon dioxide, it now appears safe to dismiss oxidation as the disturbing factor, for oxidation of amino-groups is not easy in acid solution and, moreover, the carbon dioxide is evolved from the commencement of the reaction. Also, very little nitric oxide (<1%) is in the first part of the evolved gas. This gas contains some 25% of carbon dioxide and, if oxidation were the cause of this, much more nitric oxide would be expected. It was also shown by experiment that a large excess of nitrous acid was without effect on the amount of carbon dioxide, and that the deviation of behaviour from equation (1) depended on the nitrite ion and not on the nitrous acid.

In order to minimise this nitrite ion effect (and at the same time check again the above postulates) the procedure was adopted of running the nitrite solution slowly into an acid–glycine solution. The results obtained are summarised in Table VI. When the solution was acidified with hydrochloric acid the carbon dioxide was evolved in about 10% of its former

TABLE VI.

Sodium nitrite solution slowly added to glycine (0·1 *mole*) *and* 0·12M-*acid in water* (300 *ml.*).

Acid.	N_2, l.	CO_2, l.
HCl	1·75	0·065
HCl	1·91	0·056
HOAc	2·24	0·234

quantity; but when acetic acid was employed, whilst less carbon dioxide was evolved, the quantity was considerably more than when hydrochloric acid was used. This was as expected; for the equilibrium

$$HOAc + NO_2^- \rightleftharpoons HNO_2 + OAc^-$$

lies very much to the left, and therefore much free nitrite ion is present in such a system.

The Van Slyke determination is carried out by mixing three solutions: saturated aqueous

sodium nitrite, acetic acid, and the solution containing the amine. Acetic acid is used for two reasons. First, it causes less decomposition of nitrous acid—for the above-mentioned reason that very little free nitrous acid exists in these solutions. Nitrite ion is thus in excess, and so it causes the anomalous behaviour described. Secondly, amides, urea, etc., which are usually present in biological extracts, evolve nitrogen much less readily in the absence of mineral acid. Therefore attempts to minimise the disturbances caused by nitrite ion intervention by adding the nitrite solution to the amino-acid solution acidified with mineral acid (Table VI) would be unsatisfactory.

It was also noted that very little nitrous oxide was evolved when a glycine–sodium nitrite solution was rapidly acidified. This was due to the removal of nitrous acid from the solution (free nitrous acid rapidly decomposes). The hydroxylamine was shown to be held in solution as the hydrochloride.

From the foregoing, it is clear where the discrepancy lies in the Van Slyke determination of glycine. Although only one amino-acid has been studied here, it seems probable that the above series of reactions will apply in principle to α-amino-acids generally, although the influence of adjacent groups in the higher members has yet to be ascertained. This influence may manifest itself with the higher amino-acids, such as alanine, etc., mainly by virtue of the reduction in the number of α-hydrogen atoms. The changes subsequent to the formation of nitro-compound may be impeded and nitrosation, which is so important in the rapid decarboxylation of glycine (p. 153), may not be possible. The amount of gas evolved with alanine, etc., is very close to that predicted by equation (1) and so permits the use of the Van Slyke determination, but it is almost certain that corresponding nitro-compounds are formed to a large extent and so the chemistry of the change is not represented by this equation. Glycine has always been recognised as one of the amino-acids least suitably determined by this method, and many attempts have been made to remove the anomaly of " too much " nitrogen. Kendrick and Hanke (*J. Biol. Chem.*, **1937**, **117**, 161) claimed that the addition of potassium iodide or iodine eliminated the excess of nitrogen. This was disputed by Dunn and Porush (*ibid.*, **1939**, **127**, 261) but reiterated by Kendrick and Hanke (*ibid.*, **1940**, **132**, 739). They considered that the effect was caused by preferential oxidation by the iodine (with the result that nitrous acid was not reduced to nitrogen); but in view of the established nature of the glycine reaction it would be better to defer an explanation of the iodine effect until the reaction of iodine with the now known intermediates has been established.

The present investigation gives an explanation of the abnormal kinetic results of Abel, Schmid, and Sidon (*Z. Elektrochem.*, **1933**, **39**, 863) in their investigation of glycine; it was found that as the nitrite-ion concentration was increased the velocity coefficient of the reaction increased several-fold. This was attributed to specific electrolyte effect on the amphoteric glycine (carbon dioxide was not tested for in the evolved gas, all of which was assumed to be nitrogen).

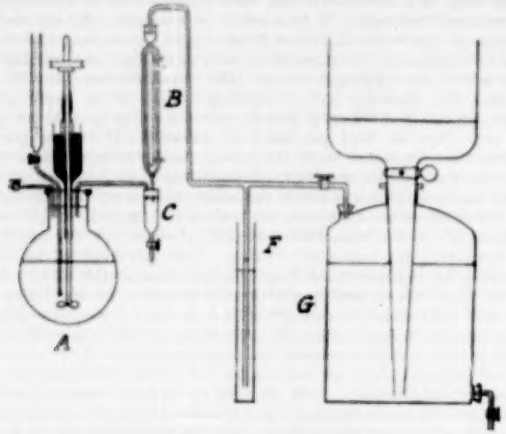
Viscontini (*Helv. Chim. Acta*, **1946**, **29**, 1491) found that reaction of nitrous acid with polyglycines, such as glycylglycine, yielded very little of the expected hydroxy-compound, $HO{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$, but a large amount of oxalylglycine, $HO_2C{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$. The evolved gas contained very little carbon dioxide, but the nitrogen was 160% of that expected from the usual equation. These facts may now be interpreted on the assumption that the corresponding nitro-compound is formed, followed by nitrosation, giving $O_2N{\cdot}C(N{\cdot}OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$ which decomposes to oxalylglycine. It seems probable that nitrous oxide formed part of the gas evolved, but this was not tested.

It may be asked: " Where does the sequence of reactions stop under the conditions of the Van Slyke determination of glycine? " No proper answer can be given, but the considerable frothing that occurs indicates that part, at least, of the nitrolic acid has reached and passed the trifulmin stage. Concerning the gas evolution it may be said that there is a very rapid primary evolution of nitrogen (nitrous acid elimination of the amino-group of the amino-acid) accompanied by a fast evolution of carbon dioxide (from decarboxylation of the nitrosated nitro-acid). The secondary nitrogen and carbon dioxide, as well as the nitrous oxide, are formed at the end of the series of reactions (p. 153) and, at ordinary temperatures, this gas evolution is comparatively slow. The specified time in a Van Slyke determination is about 4 minutes (according to the temperature), and it can only be said that the stage reached in the gas evolution will at this time be somewhere just after the steep part of the curve in Fig. 1.

Experimental.

The apparatus used for measuring the gas evolution is shown in Fig. 2. Glycine (0·1 mole) and the appropriate amount of sodium nitrite were dissolved in water (300 ml.) in the flask *A* immersed in the thermostat. The whole apparatus was filled with nitrogen from a cylinder, and then standard acid (2*N*.) was slowly added from the burette (time of addition approx. 40 minutes). The evolved gas was collected in *G* over saturated aqueous sodium chloride, which was also saturated with the relevant gases. After a fixed interval of time (2—3 hours in different experiments) the thermostat was removed and the contents of flask *A* were heated to boiling. The ice-coldwater-condenser *B* re tained steam, and this condensate was collected in the container *C*. Hydrochloric, sulphuric, and acetic acid were used and no difference was observed (other than the blue colour when hydrochloric acid was used). The preliminary reaction (*i.e.*, before the heating) was carried out at 0°, 16°, or 25°, again with no significant difference (although the green colour that developed was more intense the lower the temperature) and 16° was chosen for convenience in the final investigation.

Fig. 2.



The gas analyses were carried out on samples (35—45 ml.) taken from the gas collectors and brought into contact successively with small volumes of concentrated absorbents in gas-burettes. Acid ferrous sulphate was used to remove nitric oxide, potassium hydroxide for carbon dioxide, and ethyl alcohol for nitrous oxide. The residual gas was assumed to be nitrogen. Tests for carbon monoxide were negative. Because of its solubility in most reagents the presence of nitrous oxide makes the analyses somewhat uncertain, but by the use of small volumes of concentrated reagents the error due to this was kept low. That the gas removed by the ethyl alcohol was nitrous oxide was proved by passing the original gas (after removal of nitric oxide and carbon dioxide) through a trap immersed in liquid air. A white solid was retained. On removal of the trap from the liquid air this white solid melted to a colourless liquid which boiled at a very low temperature, and the evolved gas remained colourless in the presence of oxygen. Samples were evaporated into a eudiometer, mixed with hydrogen (1·8—2·5 volumes), and exploded according to the method of Menzel and Kretzschmar (*Z. angew. Chem.*, 1929, **42**, 148). The contractions observed were exactly equal to the original volume of gas sample: $N_2O + H_2 \longrightarrow H_2O + N_2$.

Materials.—Glycine used in the above experiments was recrystallised from aqueous alcohol and contained no detectable impurities. Analysis by the Sörensen formaldehyde method gave results identical with 3 other samples of AnalaR glycine.

Potassium nitroacetate was prepared from nitromethane (Steinkopf and Kirchhoff, *Ber.*, 1909, **42**, 3925) and, when recrystallised several times (50% aqueous potassium hydroxide) and washed with ethyl alcohol, was pale yellow. It was quite stable when kept *in vacuo*. It proved more convenient to use the potassium salt rather than the free acid, the preparation of which required the extra steps given by Pedersen (*Trans. Faraday Soc.*, 1927, **23**, 316). The acid, after recrystallisation from chloroform, melted at 93—93·5° (lit., 87—89°).

Methylnitrolic acid was prepared from nitromethane by the method of Wieland (*loc. cit.*). It is an unstable compound, m. p. 64—66° (decomp.), and could not be kept for more than a few hours. The aqueous solution soon decomposed and the gas measurements obtained with this (Table III) are not as decisive as those obtained using potassium nitroacetate.

Formohydroxamic acid, prepared from ethyl formate and hydroxylamine (Jones, *Amer. Chem. J.*, 1895, **20**, 28), formed white glistening plates, m. p. 80°.

Isolation of Nitromethane from the Glycine–Nitrous Acid Reaction.—The success of this experiment depends on the very slow addition of acid to the glycine–sodium nitrite solution in order to avoid a local excess of nitrous acid and so to enable the nitroacetic acid to decompose to nitromethane. Glycine (0·5 mole) and sodium nitrite (4 mole) in water (500 ml.) were slowly acidified (150 ml. of 2*N*-sulphuric acid) during 3 hours. An hour after completion of the acidification the solution was distilled. Oily droplets were visible in the early portions of the distillate, and distillation was continued until 150 ml. were collected. The distillate was neutralised and then fractionated using an ordinary disc-column. Between 75° and 95° a colourless 2-phase liquid was collected (total volume, 10 ml.). The lower phase (~2·5 ml.) was separated. With nitrous acid it gave the nitrolic acid test for nitromethane and, after being dried ($MgSO_4$), had b. p. 100—102° (micro-method) (nitromethane has b. p. 101°) (Found: C, 20·1; H, 5·5; N, 22·4. Calc. for CH_3O_2N: C, 19·7; H, 4·9; N, 22·9%). The refractive index was identical with that of a carefully purified specimen of nitromethane.

Isolation of Methylnitrolic Acid from the Glycine–Nitrous Acid Reaction.—The reaction was carried out at 0° with moderately quick addition of acid, taking precautions to keep the temperature low. The solution was extracted twice with ether, the extract dried ($CaCl_2$), and the solvent removed under reduced pressure. Pale yellow needles (~2 g.), m. p. 64—66°, were obtained from a solution of glycine (0·4 mole) and sodium nitrite (1·2 moles) in 300 ml. of water when acidified by 300 ml. of 2*N*-sulphuric acid; the m. p. and reactions were identical with those of synthetically prepared methylnitrolic acid. About 5—10 ml. of a yellow oil were also obtained in the extraction (cf. p. 151). On increase of the concentration of sodium nitrite in the above experiment, there was a marked increase in the amounts of yellow solid and oil, but these experiments at higher nitrite concentrations were difficult to control because of the extensive frothing.

Identical behaviour was observed when potassium nitroacetate was used in place of glycine. Pale yellow needles, m. p. 64—66° (decomp.), and a yellow oil were obtained on ether-extraction of the reaction residue.

Formation of Trifulmin.—The white froth that formed at ordinary temperatures in both the glycine and the potassium nitroacetate experiments could be filtered off; it had the same explosive character as the substance prepared from methylnitrolic acid (Wieland, *loc. cit.*). With methylnitrolic acid the frothing was shown to commence at pH 4—5.

Isolation of Chloroacetic Acid from the Glycine–Nitrous Acid Reaction when Chloride Ions were present.—Glycine (0·3 mole), sodium nitrite (0·32 mole) and potassium chloride (2·0 moles) were dissolved in water (500 ml.), and 150 ml. of acid (2*N*.) were slowly added during 2 hours. The temperature was kept at 5°. The blue colour of the final solution was readily removed with ether, and the colourless solution was then extracted with several further lots of ether. These extracts were dried ($CaCl_2$). Evaporation of the ether yielded 11·9 g. of white crystalline material. This had an odour similar to that of acetic acid, contained "bound" chlorine, and, after recrystallisation from chloroform, had m. p. 63°, undepressed on admixture with chloroacetic acid. The material boiled without decomposition at 187—189°/765 mm. (Found: C, 25·6; H, 3·3; Cl, 37·4. Calc. for CH_3O_2Cl: C, 25·4; H, 3·2; Cl, 37·6%). The amount of recovered chloroacetic acid represents a 40% conversion of the original glycine.

Analytical Determination of Glycollic Acid in the Glycine–Nitrous Acid Residues.—The acid–alkaline permanganate method suggested by Wieland and Franke (*Annalen*, 1927, **457**, 13) with the recommendations of Bottger and Oesper ("Newer Methods of Volumetric Chemical Analysis," Van Nostrand, N.Y., 1938) was found satisfactory. It was shown, using potassium nitroacetate, that most of the products other than glycollic acid could be removed by treatment with excess of nitrous acid followed by boiling (to remove formic acid). It was shown, using glycollic acid (Kahlbaum), that the above treatment resulted in the decomposition of approx. 10% of the glycollic acid, but it was considered that the method was sufficiently accurate for the present purpose.

Other Identifications.—Hydrocyanic acid was detected in the distillates by the characteristic odour, and the white precipitate obtained with silver nitrate (soluble in ammonia, insoluble in nitric acid) darkened on addition of mercurous nitrate (dissolving in excess). Prussian blue was obtained by heating with ferrous sulphate in alkaline solution. The pungent odour obtained on continued distillation (and fractionation) was established as due to formic acid by the solubility of the silver salt of the latter, and its reduction of ammoniacal silver nitrate. Hydroxylamine was detected in the residues by its reducing properties (mercuric chloride), and the formation of ammonia on heating of the alkaline solution.

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33. *A Kinetic Study of Organic Inhibitors of the Reaction between Magnesium and Acids.*

By R. Hurst and M. A. Jermyn.

This paper extends to the system magnesium–acid, previous observations by other authors of the inhibition of metal–acid reactions by organic substances and presents simplified methods for studying the kinetics of such inhibitions.

The dissolution of magnesium by acids has been found to be inhibited by organic amines. The dissolution reaction is of zero order in the presence of excess of acid, with an energy of activation of about 4000 cals./g.-mol. which is not greatly altered by the presence of inhibitor. Various reaction-rate constants have been determined. The relation between inhibitor concentration and degree of inhibition is found to be that expected for an adsorption process. The effectiveness of the inhibitor depends on steric factors—the shape and size of its molecule regarded as adsorbed on the metal surface at an active point.

It has long been known that certain organic compounds can inhibit the attack on metallic surfaces by acids and other corroding agents. Investigations have been made into the inhibiting properties of a variety of substances, ranging from simple aliphatic amines to large colloidal molecules, chiefly with a view to practical application. From this body of data the following widely-accepted generalisations have been drawn. First, organic inhibitors act only in so far as they are adsorbed on the metal surface, since it is found that the activity of the inhibitor in depressing the reaction rate when expressed as a function of its concentration is a typical adsorption isotherm (Mann, Lauer, and Hultin, *Ind. Eng. Chem.*, 1936, **28**, 159, 1046). The presence of an adsorbed film of organic base has actually been demonstrated in one case (Rhodes and Kuhn, *ibid.*, 1929, **21**, 1066). Further, compounds having inhibitor properties are either colloidal electrolytes or molecules which form co-ordination complexes (*e.g.*, amines, ethers, thio-compounds, unsaturated hydrocarbons). Secondly, closely related compounds, though held to the metallic surface by the same active group, have widely different inhibiting powers. These differences may be explained by steric factors—an inhibitor molecule blankets an area of the metallic surface dependent on its shape and size.

Very little work has been done to elucidate the exact mechanism of these inhibitions; indeed, there is still no general agreement on the mechanism of the primary reaction between metals and acids which, like many heterogeneous reactions, has complicated kinetics unless simplifying conditions are chosen. It is only under similar simplified conditions that we can hope to obtain an insight into the mechanism of the inhibited reaction. A simple molecule as the inhibitor and a highly electropositive metal dissolving in a dilute strong acid provide the simplest conditions possible and help the theoretical analysis of the problem even though efficient "inhibition" in the practical sense is not achieved.

Experimental.

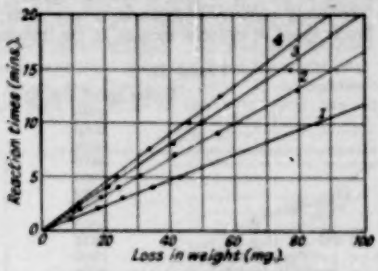
Hollow cylinders of magnesium, 2·0 cm. long and 0·9 cm. in diameter, were turned from rods of the pure metal. The preparation of the surface was found to be the most important single factor affecting reproducibility of the rate constants. Chemically etched surfaces gave erratic results and only mechanically polished surfaces were satisfactory. The cylinder was cleaned from oxide and grease and then polished with superfine emery paper. Particles of abrasive and metal were swabbed off with cotton-wool moistened with alcohol. Re-preparation of the surface was necessary after each run, especially when strongly inhibiting solutions were used. Reproducibility of $\pm 2\%$ was obtained with the same cylinder when prepared in this way. After being weighed, a prepared cylinder was secured to an ebonite rod passing through it by ebonite nuts and rubber washers at each end, and the whole was screwed together tightly so that only the external cylindrical surface was exposed. The rod was held vertically in a chuck which could be rotated at high speed through gearing from a constant-speed motor and which could be raised and lowered while rotating. The corrosive solution (500 c.c.) was placed in a bolt-head flask immersed in a thermostat kept at the desired temperature to within $\pm 0{\cdot}05°$, and allowed to come to bath temperature. The motor was then started, and after reaching constant speed the rod and cylinder were lowered into the solution. At the end of the reaction period the rod was raised and a stream of water played on the cylinder as it slowed down. The detached cylinder was then washed thoroughly with distilled water, dried in a stream of warm air, and weighed. The raising and lowering of the cylinder occupied less than a second each in the usual total time of four minutes.

According to various workers (King and Cathcart, *J. Amer. Chem. Soc.*, 1937, **59**, 63; King and Schack, *ibid.*, 1935, **57**, 1212; Durdin and Markovitch, *J. Gen. Chem. Russia*, 1936, **6**, 236; Kilpatrick and Rushton, *J. Physical Chem.*, 1930, **34**, 2180), the reaction in the presence of a large excess of acid is of zero order. To check this under our conditions the same cylinder, freshly prepared each time, was rotated for various periods in an acid solution. Results obtained in a sodium acetate–hydrochloric acid mixture (pH = 1·09; see Walpole, *Biochem. J.*, 1914, **8**, 637) in 0·1*N*-acetic acid and in 0·1*N*-sulphuric acid are shown graphically in Fig. 1. In each case the loss in weight is proportional to reaction time, and it is therefore legitimate to take the loss during any convenient time as a measure

of the rate constant. In all further experiments a period of 4 minutes was used, long enough to give an accurately weighable loss of metal, but not enough to change the diameter of the cylinder appreciably, or the amount of acid present.

FIG. 1.

Loss of weight of magnesium cylinders in acid solution at 25°.



1. 2 × 0·9 *cm.*, 2150 *r.p.m. in* 500 *c.c.* 0·1N-H_2SO_4.
2. 2 × 0·9 *cm.*, 1300 *r.p.m. in* 500 *c.c.* 0·1N-H_2SO_4.
3. 2 × 0·9 *cm.*, 1300 *r.p.m. in* 500 *c.c. acetate–*HCl *mixture* (pH = 1·09).
4. 3 × 0·9 *cm.*, 2150 *r.p.m. in* 400 *c.c.* 0·1N-*acetic acid.*

In order to extend the above procedure to the measurements of inhibiting power, a given cylinder, after duplicate runs in fresh portions of the acid solution, was again run twice in portions of acid to which the desired concentration of inhibitor had been added. The ratio

$$\frac{\text{Average loss in weight in solution with inhibitor}}{\text{Average loss of weight in pure acid solution}} \times 100$$

was termed the "relative corrosion," and was independent of actual loss of weight, which varied slightly from cylinder to cylinder since the dimensions were not all the same. The simple aliphatic amines are not very efficient inhibitors of the metal–acid reaction, and with magnesium and strong acids it was found that the main effect of adding the base was neutralisation. The reactions were therefore carried out in the sodium acetate–hydrochloric acid mixture referred to above. Large additions of amine could be made to it without sensible alteration of its pH of 1·09. Heterocyclic nitrogen compounds were much better inhibitors. Typical results are given in Table I, piperidine being the inhibitor.

TABLE I.

Acid : NaOAc–HCl mixture. Inhibitor : piperidine.
Time : 4 minutes. Temperature : 25°.

Concn. of inhibitor m.-mols./l.	Loss of wt. in acid (g. × 10^{-4}).			Loss of wt. in acid plus inhibitor (g. × 10^{-4}).			Relative corrosion.
5	216	210	Mean 213	185	181	Mean 183	88·8
10	199	197	198	162	161	161·5	82·0
15	196	201	198·5	154	148	151	76·0
20	198	202	200	140	144	142	71·0
30	202	204	203	129	125	127	62·5
40	198	205	201·5	107	112	109·5	54·1
60	197	202	199·5	90	93	91·5	45·9
80	200	204	202	85	81	83	41·2
100	204	199	202·5	70	75	72·5	36·0

RESULTS AND DISCUSSION.

Calculation of Rate Constants.—It has been stated (King and Schack, *loc. cit.*) that the rate of reaction is directly proportional to the velocity of the surface through the solution at speeds above 1000 cm./minute. Speeds used in this study were 1300 r.p.m. and 2150 r.p.m., giving for cylinders 0·9 cm. in diameter a linear velocity through the solution of 3675 and 6080 cm./minute, respectively. The ratio obtained by comparing the slopes of curves 1 and 2 in Fig. 1 shows that in the present case the rates are roughly, but not exactly, proportional to these velocities (ratio of speeds = 1·65; ratio of reaction velocities = 1·43). Kilpatrick and Rushton's relationship (*loc. cit.*), *i.e.*, reaction velocity proportional to (speed of rotation)$^{2/3}$, gives a calculated ratio of reaction velocities of 1·157, agreeing even less well. It was decided to use King and Schack's relationship in comparing the data of the present study with those of

previous workers. The special first-order formula used in both the investigations just referred to was thus adjusted for speed of rotation and a constant k was calculated from the formula

$$k = \frac{2{\cdot}303V}{At} \cdot \log\frac{a}{(a-x)} \cdot \frac{1000}{L}$$

where V = volume of solution, in ml.; A = area of cylinder surface, in square cm.; t = time of run, in minutes; a = dissolving capacity of solution, in any units; x = amount dissolved, in the same units; L = linear speed of cylinder surface, in cm./minute.

TABLE II.

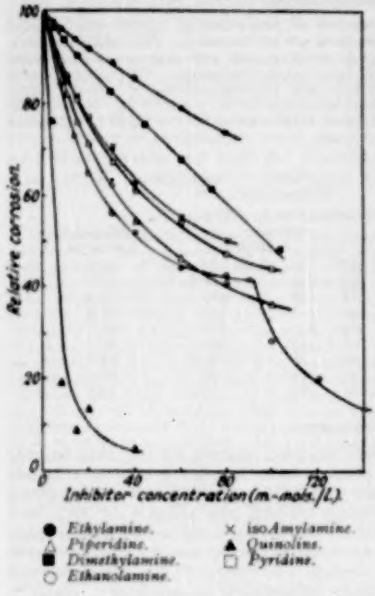
Corroding solution.		Linear speed, cm./min.	k.	Observers.*
H_2SO_4	0·05N	6080	0·205	H. and J.
,,	0·0575N	2000	0·229	K. and C.
,,	0·1N	6080	0·202	H. and J.
,,	0·1N	3675	0·242	,,
,,	0·15N	6080	0·201	,,
$CH_3{\cdot}CO_2H$	0·05N	6080	0·075	,,
,,	0·0597N	2000	0·090	K. and C.
HCl	0·05N	2000	0·248	,,
Acetate–HCl mixture (pH = 1·09)		3675	0·157	H. and J.
Pyridinium chloride (0·06M.) + pyridine (0·04M.)		2000	0·312	K. and C.
Pyridinium chloride (0·03M.) + pyridine (0·07M.)		2000	0·175	,,
Pyridinium sulphate (0·05M.) + pyridine (0·05M.)		6080	0·245	H. and J.

* K. and C. = King and Cathcart; H. and J. = present work.

This constant is then independent of volume used, concentration of acid, size of cylinder, and time of run, and reduces all results to a linear speed of 1000 cm./minutes. It has the dimensions cm./minute since the reaction is diffusion controlled. Table II gives the calculated values of k for various solutions used in the present work and also some recalculated from the work of King and Cathcart.

FIG. 2.

Relation between concentration and degree of inhibition in acetate–HCl mixture at 25°.



The table shows that the values obtained in the present work are of the same order as those obtained earlier and are in good agreement when direct comparison is possible, allowance being made for the fact that the constant is adjusted empirically for the difference in speed of rotation and is taken over only a short part of the reaction. The constant can be seen to vary with the acid used and is not directly related to the hydrogen-ion concentration. It is noteworthy that the pyridinium ion is an even more corrosive agent than the hydrogen ion and confirms the view that all the "acids" in the extended sense must be considered to take part in the reaction.

Effect of Inhibitors.—The figures for the inhibiting power of various amines in the acetate–acid mixture obtained as outlined in the experimental section are shown graphically in Fig. 2. Most of the curves are of the type to be expected if adsorption is the controlling process. The figure shows clearly the increased efficiency of inhibition due to: (*a*) increasing length of chain (compare ethylamine and *iso*amylamine), (*b*) multiplicity of chains (compare ethylamine and dimethylamine), (*c*) ring formation (compare isoamylamine and piperidine), (*d*) multiple rings (compare quinoline and piperidine).

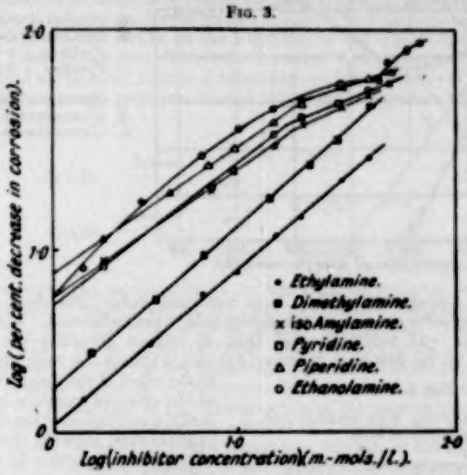
These results extend to magnesium conclusions that have been reached after detailed observations of other metals (Mann, Lauer, and Hultin, *loc. cit.*) The curve for ethanolamine shows a remarkable and reproducible anomaly; this, and the greatly increased efficiency

compared with the similar ethylamine, is probably due to solvation of the hydroxyl group, giving an enhanced blocking effect.

Erratic results were obtained with quinoline; an insoluble yellow complex was formed with magnesium salts giving an adherent coating so that this part of the work was discontinued.

If the results shown in Fig. 2 are plotted as log (% decrease in corrosion) against log (concentration of inhibitor), as in Fig. 3, it is clear that the relation $\log I = \log a + b \log c$ (where I = % decrease in corrosion, c = inhibitor concentration) is valid up to about 40% decrease in corrosion for all inhibitors studied. For this part the slope (b) is about 0·75. With isoamylamine, pyridine, and piperidine there is a second straight part of the curve with a slope of about 0·40 (cf. Mann, Lauer, and Hultin, *loc. cit.*). If we assume that the inhibiting action is controlled by adsorption from the liquid on the solid metal, the values of b are of the right

FIG. 3.



order. The break in the curve may be due to a change of packing necessary to accommodate the larger molecules, or to an overflow from primary to secondary cathodic areas according to Taylor and Rideal's theory ("Catalysis in Theory and Practice," 1922).

Temperature-coefficient Measurements.—Measurement of the rates of the inhibited and the uninhibited reactions were made over a range of temperature and the apparent energies of activation were calculated from the Arrhenius equation $k = Ae^{-E/RT}$.

The results given are the average of duplicate runs with each of four identical cylinders and are thus the mean of eight determinations. It has been shown (King and Cathcart, *loc. cit.*; King and Braverman, *J. Amer. Chem. Soc.*, 1932, **54**, 1744; King, *ibid.*, 1935, **57**, 828) that the observed energy of activation for the dissolution of metals by strongly acid solutions is probably, in fact, an energy of diffusion; the values found agree with that to be expected for a diffusion energy and are extremely low for a true activation energy. The mean energy of activation found in this study (3800 cals./g.-mol.) agrees with that found by other observers.

Whatever the mechanism, it is obvious from Table III that it is not inherently altered by the presence of inhibitors. Areas of surface are apparently blocked off, but the residual reaction is the same as before.

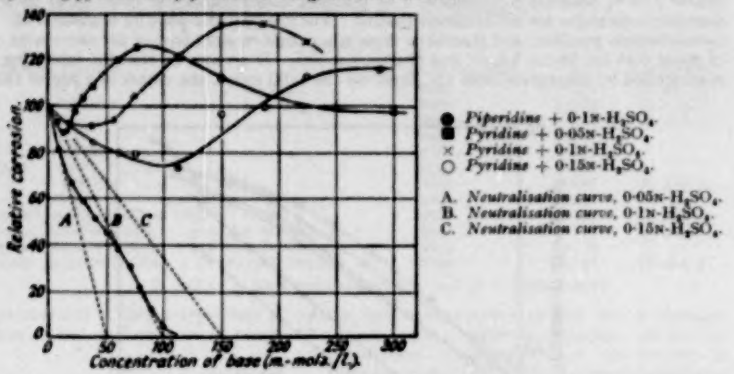
TABLE III.

Concn. of inhibitor (m.-mols./l.).	Loss of wt. (10^{-4}g.) at: 18°.	25°.	35°.	45°.	Energy of activation (cals./mol.): 25°/18°.	35°/25°.	45°/35°.	Mean.
0	158	199	245	296	3950	3790	3680	3800
20	—	154	197·5	248	—	4550	4450	4500
40	—	129·5	165	204	—	4460	4300	4380
60	—	107·5	135·5	167	—	4230	4170	4200
80	—	94	118	145	—	4160	4080	4120
100	—	84·5	105	128	—	3960	3820	3890

The apparent energy of activation is in all cases about 4000 cals./g.-mol. but shows a tendency to decrease with rise of temperature, for both the inhibited and the uninhibited reactions. There is also a sharp increase with the first increment of inhibitor, but with succeeding additions the energy decreases and approaches the value for the uninhibited reaction.

FIG. 4.

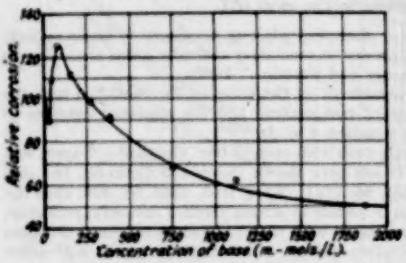
Effect of adding pyridine and piperidine to unbuffered acid solutions.



Experiments in Unbuffered Solutions.—As remarked earlier, the chief effect of adding a basic amine to an unbuffered solution of a strong acid is neutralisation. Thus the experimental curve for piperidine and sulphuric acid (Fig. 4) follows generally the theoretical curve for neutralisation. In the first part, however, the rate is always less than the theoretical, owing to the effect of the concurrent adsorption, but at the point of complete neutralisation, there is still a residual reaction equal to 4·6% of the original rate, showing that the piperidinium cation itself is acting as an "acid" in the extended sense.

FIG. 5.

Extended version of Fig. 4 for pyridine and 0·05N-sulphuric acid.



The experimental curves for pyridine show this effect even more clearly (also on Fig. 4). At the neutral points for three acid strengths it was found that the resulting pyridinium sulphate was more corrosive than the original sulphuric acid. Results obtained on adding extremely large amounts of pyridine to 0·05N-sulphuric acid are shown in Fig. 5.

Even when the solution was 1·8M. with respect to the pyridine, the reaction rate was still 50% of the uninhibited rate. Thus both faintly acid (pyridinium sulphate) and faintly basic (pyridinium sulphate and pyridine) solutions show high reactivity, and this can only be interpreted as showing that the pyridinium ion itself is active in the metallic dissolution process. The curves of Fig. 4 and 5 therefore show the following effects: (*a*) initial neutralisation combined with slight inhibition, (*b*) a corrosive action by pyridinium ions which rises as the pyridinium ion/hydrogen ion ratio rises, (*c*) inhibition of pyridinium-ion corrosion by increasing amounts of pyridine. The complex nature of the interactions allows only general conclusions to be drawn and it is not yet possible to explain the shape of the curves in detail.

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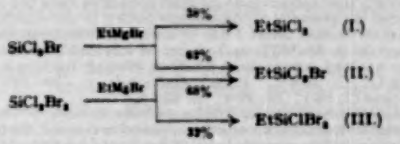
34. *Experiments on the Substitution Behaviour of the Silicon Chlorobromides.*

By C. J. Wilkins, N. P. H. Brown, and Alison D. Stevens.

Trichlorobromosilane and dichlorodibromosilane react with Grignard reagents with replacement of both chlorine and bromine, the proportion of bromine replaced being higher the larger the alkyl group. From the reactions of these silicon chlorobromides with ethylmagnesium bromide ethyldichlorobromosilane and ethylchlorodibromosilane have been isolated. Chlorotribromosilane and tetrabromosilane are unreactive towards Grignard reagents.

Although silicon tetrachloride reacts readily with alkylmagnesium bromides, experiments made in this laboratory by Lorking have shown that this reactivity does not extend to the tetrabromide, which indeed, fails to yield substitution products with methylmagnesium bromide at temperatures below 160°. Our results on the behaviour of the silicon chlorobromides towards Grignard reagents have shown that chlorotribromosilane resembles tetrabromosilane (silicon tetrabromide) in being unreactive; trichlorobromosilane and dichlorodibromosilane do, however, react. Both halogens undergo replacement, and with ethylmagnesium bromide the reactions proceed thus:



The percentages represent the atomic ratio of the two halogens from the silicon chlorobromide found in the precipitated magnesium halide from preparative experiments. Yields of the purified products (I), (II), and (III) were in similar proportions. The compounds, *ethyldichlorobromosilane* (II), b. p. 120—121°/768 mm., and *ethylchlorodibromosilane* (III), b. p. 141—143°/768 mm., are the first organo-substituted silicon chlorobromides to be reported. It has not proved possible to obtain the corresponding methyl compounds in a state of purity owing, it seems, to the proximities of the boiling points of the reactants and products.

In the series of tetrahalides examined the effect of the accumulation of bromine in reducing the reactivity not only of the bromine atoms themselves, but also of the adjacent chlorine, may well be connected with the steric influence of the rather large bromine atoms. Evidence for this view was obtained from an examination of the relative proportions of chlorine and bromine replaced from trichlorobromosilane and dichlorodibromosilane on their reaction with a series of Grignard reagents containing successively larger alkyl groups. It will be noticed from the following table that the larger the attacking group the higher the proportion of the larger halogen replaced.

Reagent.	MeMgBr.	EtMgBr.	PrⁿMgBr.	BuⁿMgCl.
Halide from $SiCl_3Br$, Cl, %	—	60	44	0
,, ,, Br, %	—	40	56	100
,, $SiCl_2Br_2$, Cl, %	52	39	5	—
,, ,, Br, %	48	61	95	—

These results, from experiments carried out on a small scale (0·01—0·02 g.-mol.) under comparable conditions, were again obtained by analysis of the precipitated magnesium halide. No attempt was made to isolate the volatile products from this series of reactions. Whilst high reproducibility could not be expected, the compositions of magnesium halide from the small-scale and preparative experiments using ethylmagnesium bromide are in reasonable accord.

Experimental.

Preparation of Silicon Chlorobromides.—Each of these three compounds was obtained from the reaction of silicon tetrabromide with the theoretical quantity of antimony trichloride (Schumb and Anderson, *J. Amer. Chem. Soc.*, 1937, **59**, 651). A mild reaction occurred on heating the mixture, and the product was tapped off at the appropriate temperature from the head of a 14-in. (Whitmore and Lux type) fractionating column packed with Fenske helices. After re-fractionation of the product yields were about 70%.

Silicon tetrabromide itself was obtained by passing bromine vapour over powdered silicon in a silica tube heated to redness. The product was left over mercury to remove free bromine, and distilled.

Reactions with Grignard Reagents.—In experiments conducted on a preparative scale the general

procedure introduced by Kipping was followed. The reaction was carried out in an ice-cooled flask fitted with dropping funnel, stirrer, and reflux condenser. A solution of the Grignard reagent in ether was run slowly, with stirring, into the silicon chlorobromide diluted with 2—3 times its volume of ether. With trichlorobromosilane there was an immediate separation of magnesium halide, but dichlorodibromosilane was less reactive and the halide precipitate appeared only on heating the mixture under reflux. The magnesium halide was filtered off and extracted with ether, and the liquid fractionally distilled to remove ether and separate alkylated products.

In the reactions carried out on a small scale to establish the course of the substitution, equimolecular quantities of the reactants were heated under reflux until no more magnesium halide separated. The solution was then poured off, and the halide washed with hot ether and dissolved in water for analysis.

Analysis.—Chloride and bromide in admixture were determined by precipitation as silver halide, and a Mohr titration. In some instances bromide figures were checked by titration (in a separating funnel) with freshly standardised chlorine water, the titration being continued until the colour of bromine just failed to appear in successive small quantities of chloroform used as extractant. The silicon content of a compound was determined by hydrolysis in a platinum crucible containing water, followed by evaporation and ignition.

In certain cases determination of the strong acid liberated on hydrolysis sufficed to identify a compound.

The Products from Trichlorobromosilane and Ethylmagnesium Bromide.—The Grignard reagent (0·25 g.-mol.) was added to trichlorobromosilane (0·25 g.-mol.), and stirring was continued for half an hour whilst the mixture warmed to room temperature. Magnesium halide was removed and the ether distilled off. The residual liquid (about 30 c.c.) was decanted from a further small precipitate of magnesium halide, and carefully fractionated in an all-glass apparatus using the column mentioned above. The first distillation indicated the presence of components boiling in the vicinity of 80°, 100°, and 120°. Three systematic redistillations yielded about 1 c.c. of unreacted trichlorobromosilane (b. p. 80—82°), 5 c.c. of ethyltrichlorosilane (b. p. 99—102°), and 10 c.c. of *ethyldichlorobromosilane* (b. p. 120—121°) together with incompletely resolved intermediate fractions (Found, fraction b. p. 99—102°: Cl, 62·8; Br, 1·7%. Calc. for $EtSiCl_3$: Cl, 65·6%. Found, fraction b. p. 120—121°: Cl, 33·9; Br, 37·5; Si, 13·9%. $EtSiCl_2Br$ requires Cl, 34·1; Br, 38·4; Si, 13·5%).

The Products from Dichlorodibromosilane and Ethylmagnesium Bromide.—When equivalent quantities (0·4 g.-mol.) of the two reactants were mixed no reaction occurred in the cold, the Grignard reagent forming an oily lower layer. Magnesium halide separated during five hours' heating of the mixture under reflux, after which the products were isolated as before. There were obtained about 1 c.c. of unreacted dichlorodibromosilane (b. p. 105—107°), 14 c.c. of ethyldichlorobromosilane (b. p. 119·5—122°), and 4 c.c. of *ethylchlorodibromosilane* (b. p. 141—143°) (Found, fraction b. p. 119·5—122°: 0·0141 equiv. of acid per g. Calc. for $EtSiCl_2Br$: 0·0144. Found, fraction b. p. 141—143°: Cl, 13·8; Br, 61·4; Si, 11·3%. $EtSiClBr_2$ requires Cl, 14·1; Br, 63·3; Si, 11·1%.) It is suspected that the low figure for bromine in the analysis of the second ethyl compound may be due to slight further substitution of this halogen to give an impurity having similar volatility.

Attempted Methylation of Chlorotribromosilane.—The chlorobromide was heated under reflux for several hours with an ethereal solution of methylmagnesium bromide, but magnesium halide did not separate and two liquid layers remained. Next, the silicon halide and the solid Grignard reagent (0·33 g.-mol. of each) were heated at 120° for 10 hours; the recovered liquid, distilling at 125—135°, was essentially unreacted chlorotribromosilane (Found: 0·0134 equiv. of acid per g. Calc. for $SiClBr_3$: 0·0132; for $MeSiBr_3$, 0·0106; for $MeSiClBr_2$, 0·0126).

The authors thank Mr. J. Vaughan for helpful discussion. They are also indebted to the University of New Zealand for a research grant (to C. J. W.) towards the cost of chemicals.

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35. *The Reaction of Bromine Trifluoride with Oxides and Some Oxy-acid Salts.*

By H. J. EMELÉUS and A. A. WOOLF.

The reaction of bromine trifluoride with twenty-eight oxides was studied. With CuO, B_2O_3, Tl_2O_3, SiO_2, GeO_2, TiO_2, As_2O_3, Sb_2O_3, SeO_2, UO_3, and I_2O_5 oxygen evolution was quantitative: in other cases a mixture of oxide and fluoride resulted. Metaphosphates were converted quantitatively into hexafluorophosphates, but orthophosphates gave a mixture of fluorophosphate and bromofluoride. An ionic reaction mechanism involving the "acid" $BrF_2^+PF_4^-$ is postulated to explain the formation of hexafluorophosphate. Orthoarsenates resembled orthophosphates. Potassium persulphate and pyrosulphate gave fluorosulphonate, whereas the pyrosulphite, thiosulphate, and sulphate gave equimolecular mixtures of fluorosulphonate and bromofluoride. Sodium dithionite and sulphite gave only bromofluoride. The relationship between the products and the anion structure is discussed. Oxygen was liberated quantitatively from iodates and bromates but incompletely from chlorates and carbonates.

QUALITATIVE observations on the reaction between bromine trifluoride and oxides were made by Ruff and his co-workers (*Z. anorg. Chem.*, 1931, **202**, 39; 1933, **214**, 91). Oxygen was found to

be evolved, but a quantitative study of these reactions has shown that the reactivity of bromine trifluoride was over-emphasised, since for only twelve of the twenty-eight oxides examined was oxygen evolution complete. The reaction could not, therefore, be generally applied for the determination of oxygen in oxides. Certain of the quantitative reactions may, however, be of service in determining the heats of formation of bromine trifluoride and iodine pentafluoride. Thus in the case of silica the reaction is: $3SiO_2 + 4BrF_3 \longrightarrow 3SiF_4 + 3O_2 + 2Br_2$, all of the products being volatile. The same is true of arsenious oxide or the oxides of uranium. Similarly the reaction $6I_2O_5 + 20BrF_3 \longrightarrow 12IF_5 + 15O_2 + 10Br_2$, or the reaction with an iodate (see below) could be used in determining the heat of formation of iodine pentafluoride. The reaction of chlorine trifluoride with alkali-metal halides used by Schmitz and Schumacher (*Z. Naturforsch.*, 1947, **2a**, 362) to determine the heat of formation of chlorine trifluoride would not be applicable with bromine trifluoride or iodine pentafluoride because of the formation of complexes (Sharpe and Emeléus, *J.*, 1948, 2135). The criteria for ready reaction of an oxide with bromine trifluoride were that a volatile fluoride was produced, or that the fluoride formed was soluble in the reagent. Only in the reaction with vanadium pentoxide was an oxyfluoride formed; in the other cases, when attack was incomplete, the proportions of fluoride and unchanged oxide varied with the experimental conditions and had no special significance.

Salts of oxy-acids reacted readily with bromine trifluoride but the products depended on the nature of the anion. Potassium metaphosphate yielded the hexafluorophosphate, in which the co-ordination number of phosphorus was increased from four to six. The mechanism was probably ionic, the anion being first converted into phosphorus pentafluoride, which reacted in bromine trifluoride solution as $BrF_2^+PF_6^-$. This would resemble the acid $BrF_2^+SbF_6^-$ (Woolf and Emeléus, *J.*, 1949, 2865) and could undergo the neutralisation reaction, $K^+BrF_4^- + BrF_2^+PF_6^- \longrightarrow KPF_6 + 2BrF_3$. Indirect evidence for such a mechanism was provided by the fact that bismuth orthophosphate was converted by bromine trifluoride into bismuth trifluoride with complete elimination of phosphorus and oxygen. This was due to the insolubility of the bismuth fluoride in the solvent which prevented an ionic reaction with the unstable intermediate $BrF_2^+PF_6^-$. The formation of hexafluorophosphates by the reaction of metallic halides and a small excess of phosphorus pentachloride may be explained in the same way. The dry reaction between excess of potassium or sodium fluoride and phosphorus pentachloride which produces hexafluorophosphates in much lower yields (Lange, *Ber.*, 1932, **65**, 1253) probably follows an essentially different course. Orthophosphates of metals which form bromofluorides also yielded hexafluorophosphates, but the product contained unchanged bromofluoride. Sodium orthophosphate, for example, gave two molecular proportions of sodium bromofluoride and one of sodium hexafluorophosphate. Sodium bromofluoride is relatively unstable and the analytical results showed a deficit of bromine trifluoride in the product. These reactions can also occur by an ionic mechanism, the products depending on the cation : phosphorus ratio. Pyrophosphates of univalent cations, for example, should give equimolecular proportions of bromofluorides and fluorophosphates. Silver orthoarsenate gave a similar result to sodium orthophosphate, the arsenic appearing in the product as silver hexafluoroarsenate with two molecular proportions of the stable silver bromofluoride.

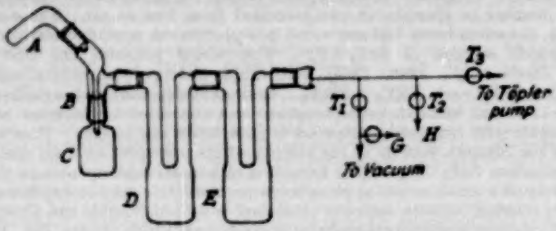
Salts of the sulphur oxy-acids reacted with bromine trifluoride in a way which was related directly to the anion structure. Potassium persulphate and pyrosulphate gave potassium fluorosulphonate, whereas potassium pyrosulphite, thiosulphate, and sulphate all gave equimolecular mixtures of the fluorosulphonate and potassium bromofluoride. The structures of these anions are known and in the case of both persulphate and pyrosulphate two S–O bonds are broken, oxygen in excess of that required to produce the SO_3F ion being eliminated. The oxygen evolution was not studied quantitatively, but it is unlikely that fluorine or bromine oxides were formed. In the bivalent pyrosulphite, thiosulphate, and sulphate ions the structures allow only one SO_3F ion to be formed and consequently one of the univalent cations was converted into the bromofluoride. The four-fold co-ordination round sulphur is retained because in an anion formed with oxygen or fluorine spatial considerations prevent a higher value being attained (Pauling, *J. Amer. Chem. Soc.*, 1933, **55**, 1895; 1927, **49**, 765). It is interesting that the pyramidal sulphite ion in sodium sulphite formed sodium bromofluoride and not sodium fluorosulphonate. Sodium dithionite also gave sodium bromofluoride as the only product. This evidence excludes the structure $[O_3S{-}S{\rightarrow}O]^{2-}$ proposed by Deines and Elstner (*Z. anorg. Chem.*, 1930, **191**, 340), since this would have given fluorosulphonate. It does not however distinguish between the structures $[O_3S{-}SO_2]^{2-}$ and $[O_3S{-}O{-}S{\rightarrow}O]^{2-}$, either of which could give bromofluoride.

Experimental.

Bromine trifluoride was prepared and purified as already described (Sharpe and Emeléus, *J.*, 1948, 2135). The oxides and salts used were whenever possible of AnalaR quality. The majority of the experiments were done in the apparatus shown in the figure, which was constructed of Pyrex glass except for the transparent silica reaction vessel *C*.

Tube *A* contained the bromine trifluoride and, together with the flask *C*, which held a weighed amount of oxide (or salt), was attached by standard ground joints to the dropping-tube *B*. Traps *D* and *E* were cooled in liquid air, and connections were made to the vacuum and Töpler pumps as shown.

Approx. 1—2 c.c. of freshly distilled bromine trifluoride were poured into *A*, which was then cooled in liquid air. Sufficient oxide to produce 50—70 c.c. of oxygen was weighed into *C* through a long funnel. While *A* was cooled and tap T_1 closed, the apparatus was evacuated slowly with T_1 and T_2 open. Traps *D* and *E* were cooled in liquid air, and *A* was allowed to reach room temperature for a short time, whereupon traces of volatile impurities in the bromine trifluoride distilled into *D*. Taps T_1 and T_2 were then closed and a known volume of pure nitrogen (*ca.* 25—30 c.c.) was passed into the reaction system from the calibrated manometer, *H*, by opening T_3; this served to prevent rapid distillation of bromine trifluoride into the cooled trap. The difference in level between *G* and *H* was observed, *C* was cooled in liquid air, and a few drops of liquid bromine trifluoride were introduced by rotating the tube *A* and partly melting its contents. The vessel *C* was warmed to initiate reaction, and further additions of bromine trifluoride were made in the same way, the completion of reaction being indicated by the manometer level. Some reactions occurred at room temperature, others required heat, and the remainder were incomplete after refluxing the oxide with liquid bromine trifluoride for periods up to 2 hours. It was essential to avoid contact of bromine trifluoride with the silicone grease used to lubricate the ground joints.



The oxygen–nitrogen mixture was drawn off with the Töpler pump and measured, excess of bromine trifluoride distilling from *C* to *D* during the process. The residue in *C* was weighed, and the equivalent weight of the reaction product was thereby determined.

Reaction of Bromine Trifluoride with Oxides.—The oxides from which a quantitative oxygen evolution was observed were: CuO, B_2O_3, Ti_2O_3, SiO_2, GeO_2, TiO_2, As_2O_3, Sb_2O_3, SeO_2, UO_2, I_2O_5. In the case of CuO, the product was CuF_2. B_2O_3, Ti_2O_3, SiO_2, GeO_2 and TiO_2 gave BF_3, TiF_4, SiF_4, GeF_4, and TiF_4 respectively. As_2O_3 and Sb_2O_3 were converted into AsF_5 and $SbBrF_4$. SeO_2 and UO_2 gave SeF_4 and UF_6, while I_2O_5 was converted into IF_5.

For the following oxides attack by bromine trifluoride was incomplete under the conditions used: BeO, MgO, ZnO, CdO, HgO, CaO, Al_2O_3, CeO_2, SnO_2, PbO, PbO_2, ZrO_2, ThO_2, MnO_2, Fe_2O_3. The product was a mixture of metal fluoride and oxide. V_2O_5 was converted into VOF_3, and BiOCl into BiF_3.

Reaction of Bromine Trifluoride with Phosphates and Arsenates.—Potassium metaphosphate was prepared by heating AnalaR potassium dihydrogen phosphate at 600° (Found: KPO_3/KH_2PO_4, 0·866. Calc.: 0·868). About 0·7 g. was refluxed with 10 c.c. of bromine trifluoride without dissolution occurring. The solid residue after removal of excess of reagent was soluble in cold water and gave no precipitate with silver nitrate; bromide and phosphate were thus absent. The hexafluorophosphate ion was determined as the nitron salt (Lange, *Ber.*, 1928, **30**, 799) (Found: PF_6, 79·2%; equiv., 182. Calc. for KPF_6: PF_6, 78·8%; equiv., 184. Found, for the nitron salt: C, 52·3; H, 4·0; N, 12·1. Calc. for $C_{20}H_{16}N_4HPF_6$: C, 52·4; H, 3·7; N, 12·2%). For preparation of larger quantities of potassium hexafluorophosphate by this method, 5 g. of salt were obtained conveniently from 10 c.c. of reagent. Sodium metaphosphate reacted similarly, yielding the hexafluorophosphate (Found: PF_6, 85·6%; equiv., 165. Calc. for $NaPF_6$: PF_6, 86·2%; equiv., 166. Found, for the nitron salt: C, 52·3; H, 3·7; N, 12·0%).

Anhydrous sodium orthophosphate, made from AnalaR disodium hydrogen phosphate and excess of sodium hydroxide and dried at 400°, was insoluble in boiling bromine trifluoride. On evaporation of the latter in a vacuum, the residue was a mixture of sodium fluorophosphate and impure sodium bromofluoride in a 1 : 2 molecular ratio. The product was decomposed with dilute nitric and sulphurous acids in a stoppered bottle, and the bromine precipitated as silver bromide. Fluorophosphate was determined as the nitron salt, after the aqueous solution had been boiled with dilute acetic acid to remove hydrobromic acid formed in the decomposition. It was shown that nitron acetate gave no precipitate with N/6-potassium bromate. The comparative stability of hexafluorophosphate to hydrolysis by dilute sodium carbonate solution enabled the fluorine present as bromofluoride to be separately determined after hydrolysis of the mixture with this reagent (Found: Na, 14·0; Br, 29·9; PF_6, 30·5; F (as BrF_3), 31·6. Calc. for $NaPF_6 + 2NaF, 0·91BrF_3$: Na, 13·9; Br, 29·3; PF_6, 29·1; F(as BrF_3), 28·5%). The high value found for fluorine is due to partial decomposition of the hexafluorophosphate. In a blank experiment 8·2% of the total fluorine in KPF_6 was hydrolised.

Bismuth orthophosphate, prepared by double decomposition of dilute nitric acid solutions of bismuth

nitrate and sodium phosphate, gave the trifluoride as the only product of reaction with bromine trifluoride, the residue being free from bromine and phosphate. Fluorine was determined by fusion with sodium carbonate, extraction of sodium fluoride with water, and precipitation as calcium fluoride (Found : F, 21·7%; equiv., 263. Calc. for BiF_3 : F, 21·4%; equiv., 266). The oxygen evolved in the reaction was collected and measured, and corresponded to 100% of the theoretical value.

Silver orthoarsenate, prepared by double decomposition, was dried at 250° (Found : Ag, 69·7. Calc. for Ag_3AsO_4 : Ag, 69·9%). Reaction with excess of bromine trifluoride gave a clear solution from which excess of reagent was evaporated in a vacuum in the usual way. The residue gave a nitron precipitate and contained bromine and arsenic. The fluorine was determined as in the case of the product from sodium orthophosphate, silver hexafluoroarsenate being decomposed only slowly by sodium carbonate solution [Found : Ag, 40·0; Br, 19·5; F (as BrF_4), 20·0%; equiv., 822. Calc. for $AgAsF_6 + 2AgBrF_4$: Ag, 39·3; Br, 19·4; F (as BrF_4), 18·5%; equiv., 825].

Reaction of Bromine Trifluoride with Metallic Halides and Phosphorus Pentachloride.—In preliminary experiments it was found that the product from potassium chloride and a small excess of phosphorus pentachloride was a mixture containing about 46% of hexafluorophosphate, the remainder being potassium bromofluoride. Silver chloride gave a similar result. Using pentabromide in place of pentachloride the yields of hexafluorophosphate were quantitative. These and certain related reactions are being more fully studied.

Reaction of Bromine Trifluoride with Salts of Sulphur Oxy-acids.—The reaction product from potassium persulphate was analysed by decomposition with boiling alkali for the fluorine determination. Fluorine was precipitated and weighed as calcium fluoride and then converted into sulphate to provide a correction for co-precipitated calcium sulphate. The sulphate formed on acid hydrolysis was precipitated with barium chloride, and fluorosulphonate was determined as the nitron salt (Traube, *Ber.*, 1919, **52**, 1272) (Found : S, 23·3; F, 12·7; SO_3F, 72·7%; equiv., 279. Calc. for $2KSO_3F$: S, 23·4; F, 13·6; SO_3F, 71·7%; equiv., 276). The nitron salt was also analysed (Found : C, 58·2; H, 4·1; N, 13·2. Calc. for $C_{20}H_{16}N_4HSO_3F$: C, 58·2; H, 4·1; N, 13·6%). The product from potassium pyrosulphate was analysed for potassium by conversion into sulphate and for fluorosulphonate as above (Found : K, 27·5; SO_3F, 72·3. Calc. for KSO_3F : K, 28·3; SO_3F, 71·7%. Found, for the nitron salt : C, 58·2; H, 4·4; N, 13·1%).

Potassium pyrosulphite gave a mixture consisting of an equimolecular mixture of potassium bromofluoride and potassium fluorosulphonate. Bromine was determined as silver bromide after decomposition with sulphurous acid in a stoppered bottle. Fluorosulphonate was determined as the nitron salt by the same procedure as for the determination of hexafluorophosphate in presence of bromofluoride. The high result was probably due to co-precipitation of nitron hydrobromide. Sulphur was determined as barium sulphate, after reduction of the aqueous solution of product with hydrazine hydrate, decomposition of the fluorosulphonate with hydrochloric acid, and a final heating at 100° for 24 hours to remove hydrogen bromide and fluoride (Found : Br, 23·6; SO_3F, 32·0; S, 9·7%; equiv., 334. Calc. for $KBrF_4 + KSO_3F$: Br, 24·0; SO_3F, 29·6; S, 9·6%; equiv., 333).

Potassium thiosulphate was dried at 150° before use (Found : S_2O_3, 58·7. Calc. for $K_2S_2O_3$: 58·9%). The product of reaction with bromine trifluoride was an equimolecular mixture of potassium bromofluoride and fluorosulphonate (Found : K, 22·6; Br, 23·1; S, 11·2; F, as BrF_4, 22·4%; equiv., 329. Calc. for $KBrF_4 + KSO_3F$: K, 23·5; Br, 24·0; S, 9·6; F, as BrF_4, 22·8%; equiv., 333). The bromofluoride was decomposed by sodium carbonate solution without appreciable decomposition of the fluorosulphonate. Potassium sulphate gave the same product (Found : Br, 24·1%; equiv., 331. Calc. for $KSO_3F + KBrF_4$: Br, 24·0%; equiv., 333). The product from silver sulphate was similar (Found : Ag, 46·7; Br, 17·4; S, 7·2%; equiv., 468. Calc. for $AgSO_3F + AgBrF_4$: Ag, 45·9; Br, 17·1; S, 6·8%; equiv., 470).

Sodium dithionite on treatment with bromine trifluoride gave sodium bromofluoride as the only solid product (Found : Na, 13·0; Br, 44·1; F, 40·6. Calc. for $NaBrF_4$: Na, 12·9; Br, 44·7; F, 42·4%). The material used was only 85% pure with respect to the dithionite ion. The latter was determined by its reduction of ammoniacal silver nitrate to silver, which was converted into the bromide after filtration and dissolution in nitric acid. Sodium was determined as sulphate (Found : Na, 29·6. Calc. for $Na_2S_2O_4$: 26·4%), the high value being probably due to the presence of sodium sulphite and sodium chloride, the latter being used as a salting-out agent in manufacture. All of the sodium in the impure dithionite was converted into bromofluoride (Found : equiv., 408. Calc. for $NaBrF_4$ on the 29·6%-Na figure : equiv., 401). Sodium sulphite also gave the bromofluoride on reaction with bromine trifluoride, the product being free from sulphur (Found : Na, 13·7; Br, 44·1. Calc. for $NaF,0·92BrF_3$: Na, 13·5; Br, 45·1%).

Qualitative Examination by X-Ray Powder Photography of the Reaction Products from Salts of Sulphur Oxy-acids.—Specimens were sealed in Pyrex capillaries and exposed to copper $K\alpha$ radiation for approximately equal times, the filament current and voltage of the X-ray tube being maintained at constant values. The resulting films were compared by superposition. It was found that the lines obtained from the products from potassium persulphate and persulphate (Group A) were identical as regards position and relative intensity, the latter being judged visually. Those of the products from potassium thiosulphate, pyrosulphite, and sulphate (Group B) were also identical. A specimen of potassium bromofluoride was prepared from potassium chloride, and all of the lines of this compound were identified in the photographs from Group B, though all were absent in the photographs from Group A. The bromofluorides obtained from sodium carbonate and dithionite gave identical photographs.

Reaction of Bromine Trifluoride with Halogenates.—With potassium iodate the oxygen evolution was 97 and 101% of theory in duplicate experiments. The solid product was potassium bromofluoride (Found : K, 20·7; Br, 40·4; F, 38·2%; equiv., 197. Calc. for $KBrF_4$: K, 20·0; Br, 41·0; F, 39·0%; equiv., 195). Mercurous iodate, prepared by double decomposition of potassium iodate and mercurous nitrate in dilute nitric acid solution and dried at 120°, gave 100% oxygen evolution. The solid product was mercuric fluoride (Found : Hg, 83·2; F, 15·2%; equiv., 234. Calc. for HgF_2 : Hg, 84·0; F, 16·0%; equiv., 238). Thallous iodate gave an oxygen evolution of 104%. The white residue of thallic fluoride (Found : Tl, 77·9; F, 21·9%; equiv., 271. Calc. for TlF_3 : Tl, 78·3; F, 21·8%; equiv., 261) left on removal of excess of bromine trifluoride became brown in moist air and was decomposed by water to

thallic hydroxide; when dried at 120° it gave the trioxide (Found: Tl, 88·4. Calc. for Tl_2O_3: 89·5%). This confirms the observation of Hannebohn and Klemm (*Z. anorg. Chem.*, 1930, **229**, 337) who prepared thallic fluoride by the action of fluorine on the oxide.

Bromine trifluoride liberated oxygen quantitatively from manganese iodate. The product was a mixture of the bi- and the tri-fluoride together with a small proportion of combined bromine trifluoride. A typical composition was: MnF_4, 37; MnF_3, 63; BrF_3, 5. Lead iodate gave a mixture of plumbous and plumbic fluorides free from other halides and containing in successive experiments 33 and 39% of PbF_4. Cobaltous iodate similarly lost all its oxygen and gave a mixture of 64% of CoF_3 and 36% of CoF_2. In the reaction with potassium bromate the evolution of oxygen was measured and found to be complete. For potassium chlorate, however, only one third was evolved as such. The solid residue in each case was potassium bromofluoride and it is possible that the chlorate yielded chlorine dioxide or even chlorine dioxyfluoride (Schmitz and Schumacher, *Z. anorg. Chem.*, 1941, **249**, 238). The reaction between bromine trifluoride and carbonates appears from preliminary experiments to be similar, since only one-third of the oxygen was liberated as molecular oxygen. The solid products from lithium and beryllium carbonate were reagent-insoluble fluorides contaminated with a trace of solvent (Found: Li, 23·2%; equiv., 59·9. Calc. for $2LiF,0{\cdot}03BrF_3$: Li, 23·3%; equiv., 59·9) (Found: Br, 8·1; F, 74·2. Calc. for $BeF_2,0{\cdot}06BrF_3$: Br, 8·7; F, 75·0%). Sodium carbonate, however, was soluble and the bromofluoride resulted (Found: Br, 43·1; F, 42·3%; equiv., 175. Calc. for $NaBrF_4$: Br, 44·7; F, 42·4%; equiv., 179).

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36. *Afzelin (Kæmpferol-3-rhamnoside), a New Glycoside isolated from Doussié.*

By F. E. KING and R. M. ACHESON.

The principal constituent of a powdery material occluded in a sample of doussié, a timber derived from trees of the genus *Afzelia*, is *kæmpferol-3-rhamnoside*, a new glycoside to which the name *afzelin* has been given.

THE conversion of a log of doussié, the timber of various species of *Afzelia*, revealed a "shake" filled with a pale brownish-yellow powder. Part of the log including the shake was submitted to the Director of the Forest Products Research Laboratory, Department of Scientific and Industrial Research, and we are indebted to Mr. W. G. Campbell of that Laboratory for a supply of the substance and for the following note on its occurrence. "Type specimens of the wood of *Afzelia* spp. commonly show a yellow deposit in some of the pores. The large deposit in the specimen under consideration probably arose as a result of the evaporation of water from tree sap which had oozed into a large fissure or 'shake.' Shakes are caused by various agencies such as, for example, internal stresses in the standing trees, damage by lightning or by impact with other trees during felling operations."

No clue as to the composition of the powder was to be found in the literature, which is without reference to any chemical investigation of the *Afzelia* genus, but from its solubility in water and the formation of a voluminous micro-crystalline precipitate on heating with aqueous acid, the presence of a glycoside was inferred. Further investigation revealed that apart from small quantities of two unidentified substances, the principal constituent is the formerly unknown *kæmpferol-3-rhamnoside*, for which we propose the name *afzelin*.

Several kæmpferol glycosides have been described which afford rhamnose on hydrolysis (see "The Chemistry of Natural Colouring Matters," Mayer-Cook, 1943, pp. 182, 183). One of these, robinin, is of interest in that on enzymic hydrolysis (Zemplen and Bognar, *Ber.*, 1941, **74**, 1783), kæmpferol-7-rhamnoside is obtained, apparently the only kæmpferol monorhamnoside hitherto definitely characterised. Of the others, in only three, *viz.*, kæmpferitrin, lespedin, and an unnamed compound found in the flowers of Australian acacia species by Petrie (*Biochem. J.*, 1924, **18**, 957), is rhamnose the sole glycosidic component. Although the nature of its hydrolysis products was clearly established, little more is known of the acacia colouring matter and nothing appears to have been done to characterise the glycoside or determine its composition. Lespedin, on the other hand, has been fully identified, and its constitution was shown by the usual chemical methods to be kæmpferol-3:7-dirhamnoside (Hattori and Hasegawa, *Proc. Imp. Acad. Japan*, 1940, **16**, 9; Hasegawa, *Acta Phytochim.*, 1940, **11**, 299). Kæmpferitrin, the yellow pigment of *Indigofera arrecta*, also gives two molecules of rhamnose when hydrolysed (A. G. Perkin, *J.*, 1907, **91**, 435), but there is no chemical evidence to show the

position of the sugar residues. On the supposition that those flavonol glycosides which differ appreciably in their ultra-violet absorption from the corresponding aglycones are 3-glycosides, Tasaki (*Acta Phytochim.*, 1925, **2**, 119, 129) has classified kæmpferitrin as a 3-bioside, but it is evident that the argument cannot be exclusive of a 3 : *x*-dimonoside structure. Moreover, the close resemblance observed by Tasaki between the spectra of quercetin and rutin, of which the latter was later shown by Attree and A. G. Perkin (*J.*, 1927, 234) to be quercetin-3-rutinoside, weakens any conclusions which may be drawn from these measurements.

Of the crude material collected from the afzelia "shake" some 20 g. were available for investigation. Hydrolysis of a portion with 2% sulphuric acid precipitated an aglycone which was undoubtedly kæmpferol (5 : 7 : 4′-trihydroxyflavonol), but a persistent impurity depressed its m. p. to 273—275°. The glycoside was therefore dissolved in aqueous ethanol, and tannins, etc., were precipitated with lead acetate. After removal of excess of lead as sulphide, the solution was evaporated, and the residue subjected to fractional crystallisation from water. The principal fraction consisted of the yellow crystalline afzelin, having the ferric chloride reaction and strong blue-green fluorescence in sulphuric acid characteristic of kæmpferol.

Hydrolysis of the purified glycoside liberated kæmpferol, m. p. 279°, identical with an authentic specimen of the flavonol kindly provided by Professor W. Bradley, Leeds University. From the filtrate neutralised with barium carbonate, phenylhydrazine acetate precipitated an osazone shown by direct comparison to be L-rhamnose osazone, m. p. 180—181°.

The position of the sugar residue was determined by methylation with excess of diazomethane and acid hydrolysis of the glassy product, whereby a crystalline *O*-trimethylkæmpferol was obtained having the properties of 5 : 7 : 4′-trimethoxyflavonol previously synthesised by Kostanecki, Lampe, and Tambor (*Ber.*, 1904, **37**, 2098). A determination of the ultra-violet absorption of the glycoside in methanol gave $\lambda\lambda_{max.}$ 2650, 3450 A.; $\lambda_{min.}$ 2810 A.; log $\varepsilon_{max.}$ 4·39, 4·12, and log $\varepsilon_{min.}$ 4·08, respectively, in fairly close agreement with $\lambda\lambda_{max.}$ 2675, 3700 A., and log $\varepsilon_{max.}$ 4·12, 4·28, for kæmpferol (Skarzynski, *Biochem. Z.*, 1939, **301**, 150). In its lack of a maximum at 3100 A. characteristic of kæmpferol and of flavonols in general unsubstituted in the 3-position (see Skarzynski, *loc. cit.*), afzelin thus conforms to Tasaki's classification.

From the solution obtained by extracting crude afzelin with a limited quantity of boiling water a colourless crystalline *compound*, $C_{15}H_{12}O_6$, was isolated. Its properties suggest that it has a tetrahydroxydihydroflavone structure, but the amount available did not admit of its full identification. The third substance encountered has not been obtained in a homogeneous condition.

Experimental.

Isolation of Afzelin.—The light powdery solid (8·6 g.) from the afzelin shake was dissolved in warm aqueous ethanol (250 c.c.; 40%). After being filtered from wood fragments, etc., the yellow solution was treated with aqueous lead acetate (100 c.c.; 10%) until no further immediate precipitation took place (the use of basic lead acetate caused precipitation of almost all the dissolved material). The product was then centrifuged, and the filtrate saturated with hydrogen sulphide to precipitate the residual lead, after which the solution was evaporated under reduced pressure to 150 c.c. A yellow precipitate (A) (1·95 g.), m. p. 155—160°, was formed after 24 hours at 0°. The filtrate from this was further concentrated (to 80 ml.) and when left at 0° for several days gave a second yellow precipitate (B) (4·1 g.), m. p. 158—165°. Little material remained in the solution, which was then discarded.

Product (A) was treated with boiling water (55 c.c.), thereby leaving a residue consisting of fairly pure afzelin. On cooling to room temperature, the filtrate deposited a very pale yellow solid (0·4 g.), later proved to be a new compound $C_{15}H_{12}O_6$ (*q.v.*). When this had been removed, a further deposition of afzelin (0·62 g.) occurred gradually at 0°. The precipitate was collected, and the filtrate, diluted to 150 c.c., was heated to boiling with product (B). Again the undissolved solid consisted of afzelin, and a further quantity (0·85 g.) crystallised at room temperature. Cooling to 0° caused the appearance of a solid (2·4 g.), which on recrystallisation was separated into afzelin (0·5 g.), and a yellow substance (1·9 g.), m. p. 208—212° (sintering at 150°); unlike the other two products isolated, it gave in ethanol solution a yellow ferric reaction. This impure product was not further examined.

The glycoside *afzelin* crystallised from water–ethanol (4 : 1) as a hydrate consisting of yellow prisms, m. p. 172—174° (effervescence) (Found : C, 54·7, 55·1; H, 5·3, 5·3. $C_{21}H_{20}O_{10},1\frac{1}{2}H_2O$ requires C, 54·9; H, 5·0. Found, after drying at 125—130° in a vacuum : C, 57·8, 57·3; H, 5·2, 5·1; loss, 6·2. $C_{21}H_{20}O_{10}$ requires C, 58·3; H, 4·6; loss, 5·9%). A Zeisel determination showed the absence of methoxyl groups. It dissolved readily in alcohols and moderately in ether. Reduction with magnesium in alcoholic hydrochloric acid gave a red colour identical with that obtained from kæmpferol under the same conditions. Treatment with concentrated sulphuric acid changed the colour of the glycoside to orange, and it then dissolved to a yellow-green solution with an intense green-blue fluorescence; heating, which changed the colour to brown, finally caused charring. The addition of basic lead acetate to an aqueous alcoholic solution of the glycoside gave a yellow-green precipitate, but dilute lead acetate produced only an opalescence.

Hydrolysis of Afzelin.—The anhydrous glycoside (0·2002 g.) dissolved easily in hot aqueous 2% sulphuric acid (25 ml.). When the solution was refluxed for 1 hour a yellow precipitate was formed, which was collected next day, the filtrate and washings being retained.

The dried aglucone weighed 0·1324 g. (99·8% calculated on the basis of one rhamnose unit per molecule). It separated from glacial acetic acid in yellow prisms, m. p. 279°, alone or mixed with an authentic specimen of kæmpferol, m. p. 279° (Found, after drying at 110° in a vacuum: C, 62·7; H, 3·8. Calc. for $C_{15}H_{10}O_6$: C, 62·9; H, 3·5%).

The solution and washings from which the aglucone had been collected were heated on a steam-bath and neutralised with barium carbonate. After removal of the precipitated sulphate the liquid was evaporated, giving a brownish gum (0·0833 g.), which was dissolved in hot water (8 c.c.). A test portion of the solution reduced hot, but not cold, Fehling's solution. Aqueous phenylhydrazine acetate (0·4 c.c. of a mixture containing 10 c.c. of phenylhydrazine and 10 c.c. of acetic acid diluted to 25 ml. with water) was added, and after 10 minutes at 100° a precipitate formed (required for the formation of rhamnose osazone, 9 minutes). One hour later the mixture was cooled, and the osazone collected. Its crystalline form was identical with that of a specimen similarly prepared from L-rhamnose, and after crystallisation from ethanol it had m. p. and mixed m. p. 180—181° to a deep red liquid (Found: C, 62·3; H, 6·5. Calc. for $C_{18}H_{22}O_4N_4$: C, 63·1; H, 6·4%).

Methylation of Afzelin.—The glycoside (0·3 g.) in methanol solution (20 ml.) was repeatedly treated with ethereal diazomethane until the solution no longer gave a green colour with alcoholic ferric chloride. The pale brown gum obtained after removal of the solvent could not be induced to crystallise; it was therefore hydrolysed by boiling for 2 hours with 2% sulphuric acid (35 c.c.). Next day, the precipitate was collected, and after 3 crystallisations from aqueous ethanol it formed very pale yellow needles, m. p. 151° (Found: C, 62·6; H, 5·8. Calc. for $C_{18}H_{16}O_6,H_2O$: C, 62·4; H, 5·2. Found, after drying at 135° in a vacuum: C, 65·4; H, 5·1; loss, 5·6. Calc. for $C_{18}H_{16}O_6$: C, 65·85; H, 4·9; loss, 5·2%). The compound was evidently 3-hydroxy-5:7:4′-trimethoxyflavone, m. p. 151—152°, synthesised by Kostanecki, Lampe, and Tambor (*loc. cit.*), and gave identical reactions with dilute sodium hydroxide and concentrated sulphuric acid, and a dull reddish-black colour with ferric chloride in ethanol.

The Compound $C_{11}H_{10}O_4$.—The pale yellow solid (0·4 g.) obtained in the course of purifying afzelin dissolved completely in boiling water (33 c.c.) and on cooling crystallised in colourless needles. After two further crystallisations it melted at 225—227° to a deep-red liquid, after becoming yellow at 200° (Found: C, 55·6, 55·1; H, 5·0, 5·0. $C_{11}H_{10}O_4,2H_2O$ requires C, 55·6; H, 4·9. Found, after drying at 110° in vacuum: C, 62·2, 62·7; H, 4·3, 4·5; loss 10·7. $C_{11}H_{10}O_4$ requires C, 62·5; H, 4·2; loss, 11·1. Ultra-violet light absorption in methanol $\lambda_{max.}$ 2900 A., log $\varepsilon_{max.}$ = 4·24; $\lambda_{min.}$ 2510 A., log $\varepsilon_{min.}$ = 3·37; inflection at *ca.* 3270 A.). It contained no methoxyl groups. It dissolved very easily in ethanol, and the solution gave a dull red ferric colour. The *compound* was stable to boiling 2% aqueous sulphuric acid. It dissolved in the cold concentrated acid to a yellow solution devoid of fluorescence even under ultra-violet light. The colour was discharged by a trace of concentrated nitric acid; on heating it became red and finally darkened from charring. The compound reacted immediately with bromine in acetic acid, and dissolved in aqueous sodium hydrogen carbonate (3%) to a very pale yellow solution. Addition of sodium hydroxide deepened the colour, and the addition of acid regenerated the compound unchanged. It slowly reacted with alcoholic 2:4-dinitrophenylhydrazine to give a crystalline precipitate; reduction with magnesium in ethanolic hydrochloric acid gave a pink colour, lighter than that similarly obtained from kæmpferol or afzelin. A derivative separating from ethanol in colourless needles, m. p. 160—164°, was obtained by the action of boiling acetic anhydride and pyridine, but the amount was too small for purification.

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37. *Fluorescent Reagents. Acyl Chlorides and Acyl Hydrazides.*

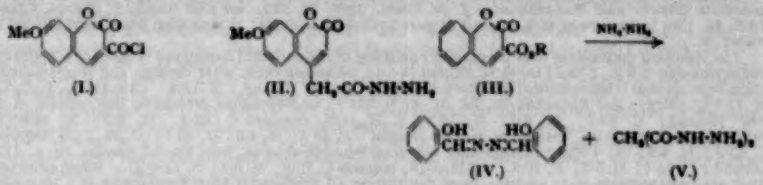
By WILSON BAKER, C. N. HAKSAR, and J. F. W. MCOMIE.

The paper describes some fluorescent acyl chlorides and hydrazides derived from coumarin-carboxylic acids, and a number of their derivatives formed by reaction with alcohols, amines, and carbonyl compounds. The fluorescence of these derivatives is designed to aid their separation by chromatographic methods. The two best reagents are 7-methoxycoumarin-3-carboxylic chloride (I), and 7-*methoxycoumarin*-4-*acethydrazide* (II).

IN a recent paper (*J.*, 1949, S 12) Baker, Collis, and Banks described some acid chlorides derived from 7-hydroxycoumarin (umbelliferone). These were prepared as fluorescent acylating agents for hydroxy- and amino-compounds, the separation and identification of which by chromatographic methods might thereby be facilitated. The most promising of these acyl chlorides was 7-methoxycoumarin-3-carboxylic chloride (I); the related esters and amides exhibit strong blue fluorescence in solution or when adsorbed on alumina, but the preparation of the reagent required the not very readily accessible 2-hydroxy-4-methoxybenzaldehyde. The present paper deals with other fluorescent reagents; no acid chloride superior to (I) has been found, but 7-*methoxycoumarin*-4-*acethydrazide* (II) is an excellent reagent for carbonyl compounds, and is very easily prepared.

Derivatives of Salicylic Acid.—*o*-Anisoyl chloride gives weakly fluorescent esters and amides.

o-Hydroxybenz- and o-anis-hydrazide readily yield with a variety of aldehydes and ketones crystalline condensation products which show a rather weak blue fluorescence in ultra-violet



light. Acetaldehyde and propaldehyde gave resinous products only. *o*-Hydroxybenzoylazide (Bondi, *Z. physiol. Chem.*, 1907, **52**, 173) is unstable, but reacts with amino-acids to give their acyl derivatives (Bondi, *loc. cit.*), which are also fluorescent. Derivatives of nitrosalicylic acids are not fluorescent.

Derivatives of Coumarin-3-carboxylic Acid (III; R = H).—This acid, its chloride, esters, and amides are moderately fluorescent in ultra-violet light, but the fluorescence is much less intense than that shown by 7-methoxycoumarin-3-carboxylic acid and derivatives.

Unsuccessful attempts have been made to prepare coumarin-3-carboxyhydrazide. Methyl and ethyl coumarin-3-carboxylates (III; R = Me or Et) fail to react with aqueous-alcoholic hydrazine hydrate at room temperature, but at the boiling point they yield a mixture of *o*-hydroxybenzylideneazine (salazine) (IV) and malonhydrazide (V). This reaction formally involves the breakdown of the α-pyrone ring, under the influence of the strongly basic hydrazine, into the components from which it was formed, namely salicylaldehyde and a derivative of malonic acid. Although coumarin-3-carboxyl chloride readily yielded the amide by treatment with aqueous ammonia, it did not give the hydrazide on treatment with the much stronger base hydrazine hydrate; the only product isolated from the viscous reaction mass was *o*-hydroxybenzylideneazine.

Derivatives of 7-Methoxy-4-methylcoumarin-3-carboxylic Acid.—In attempting to prepare the chloride of this acid by the action of thionyl chloride, Baker, Collis, and Banks (*J.*, 1949, S 12) obtained only 7-methoxy-4-chloromethylcoumarin-3-carboxyl chloride, m. p. 198—200°. Repetition of this experiment has, however, now yielded the expected 7-methoxy-4-methylcoumarin-3-carboxyl chloride, which is rather unstable and melts at 94—95°; it was identified by conversion into the known, related methyl and ethyl esters. The original formation of the chloro-acid chloride was probably due to impurity in the thionyl chloride. Thus it has now been found that 7-methoxy-4-methylcoumarin-3-carboxylic acid is converted into the chloro-acid chloride by reaction with sulphuryl chloride in presence of a trace of benzoyl peroxide as catalyst (see Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2142).

Methyl 7-methoxy-4-methylcoumarin-3-carboxylate reacts with hydrazine hydrate to give *7-methoxy-4-methylcoumarin-3-carboxyhydrazide*, and this reagent gives strongly fluorescent derivatives with carbonyl compounds.

Derivatives of 7-Hydroxycoumarin-4-acetic Acid.—This acid was originally prepared by Burton (*Annalen*, 1891, **261**, 167) by condensing resorcinol with acetonedicarboxylic acid in presence of concentrated sulphuric acid, and later the procedure was simplified by Dey and Row (*J. Indian Chem. Soc.*, 1924, **1**, 112) who condensed resorcinol directly with citric acid in presence of sulphuric acid. A careful study of this reaction with particular attention to temperature control has raised the yield of 7-hydroxycoumarin-4-acetic acid to 80%. This acid and all derivatives are intensely fluorescent, even in daylight. *Methyl 7-hydroxycoumarin-4-acetate* proved very stable towards hydrazine hydrate, and the related hydrazide was not obtained.

Methylation of 7-hydroxycoumarin-4-acetic acid with methyl sulphate and alkali gave 7-methoxycoumarin-4-acetic acid. Resinous material only was obtained in attempts to prepare 7-methoxycoumarin-4-acetyl chloride, a result doubtless due to the highly reactive nature of the methylene group. The methyl ester was prepared by direct esterification, and yielded *7-methoxycoumarin-4-acethydrazide* (II) by reaction with hydrazine hydrate. Condensation of (II) with a variety of carbonyl compounds gave the corresponding highly fluorescent *acylhydrazones*.

Experiments with disc chromatograms of alumina have shown the possibility of separating mixtures of the fluorescent esters and hydrazones described.

Experimental.

Derivatives of o-Hydroxybenzhydrazide.—This hydrazide was prepared in 73% yield from methyl salicylate (Struve and Radenhausen, *J. pr. Chem.*, 1895, **52**, 239; see also Bondi, *Z. physiol. Chem.*, 1907, **52**, 170) by the use of 60% instead of pure hydrazine hydrate; it separated from ethyl alcohol in plates, m. p. 147°.

The following derivatives were prepared by addition of the carbonyl compound (1 mol.) to *o*-hydroxybenzhydrazide (0·3 g., 1 mol.) in warm alcohol (5 c.c.), collecting them after cooling, and recrystallising them from alcohol: benzylidene derivative, needles, m. p. 248° (Found: N, 11·8. Calc. for $C_{14}H_{12}O_2N_2$: N, 11·7%) (Struve and Radenhausen, *loc. cit.*, m. p. 232°); *isopropylidene* derivative, fine needles, m. p. 228° (Found: C, 62·7; H, 6·2; N, 14·8. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·3; N, 14·6%); *piperonylidene* derivative, needles, m. p. 270° (Found: C, 63·3; H, 4·3; N, 10·1. $C_{15}H_{12}O_4N_2$ requires C, 63·4; H, 4·2; N, 9·9%); *acetophenone o-hydroxybenzoylhydrazone*, fine, fibrous needles, m. p. 212° (Found: C, 71·1; H, 5·7; N, 10·8. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%). When adsorbed from alcoholic solution on to alumina these derivatives all exhibited a blue fluorescence in ultra-violet light. Acetaldehyde and propaldehyde did not yield solid derivatives under the above conditions.

Hydrazide of 5-Nitrosalicylic Acid.—Nitration of methyl salicylate by the method of Barany and Panka (*J.*, 1946, 965) gave not only methyl 5-nitrosalicylate, m. p. 99° from ether (40% yield), but also methyl 3-nitrosalicylate, m. p. 132° (25%), from methyl alcohol, separated by taking advantage of its very sparing solubility in ether. Methyl 5-nitrosalicylate (1 g.), in methyl alcohol (20 c.c.), was shaken and then refluxed for ½ hour with 60% hydrazine hydrate (1 c.c.), cooled, and the solid collected and crystallised from methyl alcohol. The *hydrazide* formed yellow needles, m. p. 154° (decomp.) (Found: C, 42·4; H, 4·9; N, 18·4. $C_7H_7O_4N_3CH_3{\cdot}OH$ requires C, 41·9; H, 4·6; N, 18·3%).

o-Anisohydrazide and Derivatives.—Methyl *o*-anisate (30 g., 1 mol.) (Sachs and Harold, *Ber.*, 1907, **40**, 2718) and 60% hydrazine hydrate (26 c.c., 1·5 mols.) were refluxed for 2½ hours and then cooled, and the solid was collected after some hours, washed with ether, and crystallised from benzene, giving *o-anisohydrazide* (18 g., 60%) as fine needles, m. p. 85° (Found: C, 58·0; H, 5·9; N, 17·2. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0; N, 16·9%). The following derivatives were prepared by warming the reactants in alcoholic solution, completing the separation of solid by addition of water, and crystallising the products from dilute ethyl alcohol: *benzylidene* derivative, prismatic needles, m. p. 176° (Found: C, 71·0; H, 5·4; N, 11·1. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%); *isopropylidene* derivative, needles, m. p. 218° (Found: N, 13·8. $C_{11}H_{14}O_2N_2$ requires N, 13·6%). These compounds, when adsorbed on to alumina, showed a blue fluorescence in ultra-violet light. Crystalline derivatives were not obtained from *o*-anishydrazide and acetaldehyde or propaldehyde.

Derivatives of Coumarin-3-carboxylic Acid.—The acid chloride was prepared by refluxing coumarin-3-carboxylic acid (2 g.; Knoevenagel, *Ber.*, 1898, **31**, 2618) with thionyl chloride (15 c.c.) for 1 hour, cooling it, adding light petroleum (50 c.c.; b. p. 40—60°), collecting the solid, and crystallising it from benzene; it formed needles (1·7 g.), m. p. 147° (Boehm, Schumann, and Hansen, *Arch. Pharm.*, 1933, **271**, 490, record m. p. 147—148°). It was converted into the following derivatives which have been previously prepared in other ways: amide, needles from alcohol, m. p. 274° (decomp.) (Found: C, 63·4; H, 3·7; N, 7·2. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%) (D.R.-P. 172,724 gives m. p. 268—269°; Bachert, *J. pr. Chem.*, 1917, **50**, 27, gives m. p. 236°); methyl ester, m. p. 116° (lit., m. p. 116—117°), which was also prepared by direct esterification of the acid (10 g.) in presence of hydrogen chloride (yield 11 g.); ethyl ester, m. p. 94° (lit., 94°); *n*-propyl ester, m. p. 75° (Found: C, 67·1; H, 5·2. Calc. for $C_{13}H_{12}O_4$: C, 67·2; H, 5·2%) (lit., m. p. 73°); *iso*propyl ester, m. p. 89° (lit., m. p. 89°); anilide, m. p. 248°, prepared in benzene solution (Found: C, 72·2; H, 4·2; N, 5·1. Calc. for $C_{16}H_{11}O_3N$: C, 72·5; H, 4·2; N, 5·3%) (lit., m. p. 250°); benzylamide, m. p. 154° (lit., 154°); piperidide, needles (from water), m. p. 168° (Found: C, 70·1; H, 5·7; N, 5·0. Calc. for $C_{14}H_{15}O_3N$: C, 70·0; H, 5·8; N, 5·45%) (von Werder, *Merck's Jahresbericht*, 1935—6, 98, gives m. p. 168—170°). The *p-toluidide* separates from ethyl acetate in fine, greenish-yellow needles, m. p. 230° (Found: C, 73·0; H, 4·7; N, 5·1. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7; N, 5·0%). The *morpholide* crystallises from water in fine needles, m. p. 92° (Found: C, 64·7; H, 5·6; N, 5·1. $C_{14}H_{15}O_4N$ requires C, 64·9; H, 5·4; N, 5·4%).

Reaction of Hydrazine with Methyl and Ethyl Coumarin-3-carboxylates.—No reaction occurred between alcoholic solutions of the esters and 60% aqueous hydrazine hydrate in the cold. The ester (2 g.) in alcohol (10 c.c.) was boiled under reflux for ½ hour with 60% hydrazine hydrate (2 c.c.), and after cooling, the mixture of yellow and colourless solids was collected, washed, and the former separated by solution in hot ethyl acetate. This yellow product, *o*-hydroxybenzylideneazine, separated from ethyl acetate in needles, m. p. and mixed m. p. with an authentic specimen (Borsche, *Ber.*, 1921, **54**, 668) 215° (Found: C, 69·8; H, 5·2; N, 11·4. Calc. for $C_{14}H_{12}O_2N_2$: C, 70·0; H, 5·0; N, 11·7%), and gave a dibenzoyl derivative, m. p. 189° (lit., 188—189°). The colourless compound after crystallisation from alcohol had m. p., and mixed m. p. with an authentic specimen of malonhydrazide (Curtius, Schöfer, and Schwan, *J. pr. Chem.*, 1895, **51**, 187), 152°; it further gave a dibenzylidene derivative, m. p. 226° (lit., 226°).

o-Hydroxybenzylideneazine was also obtained as the only readily isolable product by the action of 60% hydrazine hydrate upon coumarin-3-carboxylic chloride in various solvents.

Action of (a) *Thionyl and* (b) *Sulphuryl Chlorides on 7-Methoxy-4-methylcoumarin-3-carboxylic Acid.*—(a) The carboxylic acid (1 g.; Baker, Collis, and Banks, *loc. cit.*) was boiled under reflux for 1 hour with thionyl chloride (10 c.c.), excess of light petroleum (b. p. 40—60°) added, and the solid collected. A further precipitation from benzene by the addition of light petroleum gave the acid chloride as pale yellow needles, m. p. 94—95°, which rises on keeping the crystals even in a vacuum (after 24 hours the m. p. was 110—113°; after 48 hours, 180—182°). Owing to this instability the chloride was not analysed, but was identified by conversion into the methyl and ethyl esters, m. p.s and mixed m. p.s with authentic specimens, 128° and 87°, respectively.

(*b*) The acid (0·5 g.) was treated with sulphuryl chloride (5 c.c.) and a trace of benzoyl peroxide. After the vigorous reaction was over the mixture was boiled under reflux for 1 hour, and cooled, and the

solid collected after several hours, precipitated from warm toluene by the addition of light petroleum, and dried in a vacuum over sodium hydroxide. This 7-methoxy-4-chloromethylcoumarin-3-carboxyl chloride had m. p. 198°, and was shown to be identical with the material, m. p. 198—200°, previously prepared by Baker, Collis, and Banks; reaction with ethyl alcohol gave ethyl 7-methoxy-4-chloromethylcoumarin-3-carboxylate, m. p. 117° (lit., 117—119°).

7-Methoxy-4-methylcoumarin-3-carbohydrazide and Derivatives.—Methyl 7-methoxy-4-methylcoumarin-3-carboxylate (2·5 g.; Baker, Collis, and Banks, *loc. cit.*), dissolved in methyl alcohol (35 c.c.), was treated with 60% aqueous hydrazine hydrate (1·6 c.c., 2 mols.), and the solid which had separated after 3 hours was collected, washed with methyl alcohol and crystallised from methyl or ethyl alcohol. The *hydrazide* (yield 55—60%) formed pale yellow needles, m. p. 210° (Found: C, 58·4; H, 5·0; N, 11·0. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·8; N, 11·3%). The following derivatives were prepared by warming the reactants in alcoholic solution: *benzylidene*, colourless needles (from alcohol), m. p. 250° (Found: C, 67·5; H, 4·8; N, 8·2. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3%); *isopropylidene* (separated after heating for 1 hour and collected after addition of water), prismatic needles, m. p. 237°, from dilute alcohol (Found: N, 9·8. $C_{15}H_{18}O_4N_2$ requires N, 9·7%).

7-Hydroxycoumarin-4-acetic Acid.—Finely powdered citric acid (100 g.) and concentrated sulphuric acid (135 c.c.) were gently shaken for ½ hour, then slowly heated to 65—70° and maintained at this temperature for ½ hour; the evolution of carbon monoxide had then abated. After the mixture had been cooled to room temperature (½ hour) and then in a freezing mixture to about −5°, resorcinol (45 g., 1 mol.) was added (½ hour) with stirring at such a rate that the temperature remained below 5°, and then concentrated sulphuric (58 c.c.) was similarly added (½ hour), and the mixture placed in the refrigerator and next day poured into ice-water (2 l.). The solid was collected, washed, and dried, giving almost pure 7-hydroxycoumarin-4-acetic acid (83 g., 80%), m. p. 209°. Crystallisation from ethyl alcohol gave the pure acid as needles, m. p. 210°. The *methyl* ester, prepared by the Fischer–Speier method in 90% yield, crystallised from methyl alcohol in fine needles, m. p. 220° (Found: C, 61·1; H, 4·1. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%); attempts to convert it into the related hydrazide were unsuccessful.

7-Methoxycoumarin-4-acetic Acid.—This acid was prepared by Dey (*J.*, 1915, **107**, 1632) by hydrolysis of its methyl ester (itself prepared in unstated yield from 7-hydroxycoumarin-4-acetic acid, methyl sulphate, and concentrated alkali), or by condensing resorcinol monomethyl ether with acetonedicarboxylic acid. 7-Hydroxycoumarin-4-acetic acid (30 g.) was dissolved in a solution of sodium hydroxide (28 g., 5 mols.) in water (280 c.c.), and methyl sulphate (20 c.c., 1·5 mols.) added dropwise with stirring (½ hour). The mixture was heated on the water-bath for 1½ hours and then cooled, sodium hydrogen sulphite added to remove a red colour, and the whole acidified with dilute sulphuric acid (total volume *ca.* 1 l.). The 7-methoxycoumarin-4-acetic acid was collected after 2 hours, washed, and recrystallised from alcohol, giving thin prisms (18 g., 57%), m. p. 186° (lit., 187°). The methyl ester, prepared in 90% yield by the Fischer–Speier method, had m. p. 122° (lit., 122°). Unsuccessful attempts were made to prepare the acid chloride by the use of thionyl chloride under a variety of conditions, and by the action of phosphorus oxychloride on the sodium salt of the acid, but only coloured resinous products resulted.

7-Methoxycoumarin-4-acethydrazide.—To the preceding methyl ester (5 g.), dissolved in methyl alcohol (110 c.c.), was added 60% aqueous hydrazine hydrate (5 c.c.; 1·5 mols.), and the solid which separated was collected after 4 hours, washed with dilute methyl alcohol, and crystallised from methyl or ethyl alcohol, giving fibrous needles (2·8 g., 56%), m. p. 208° (Found: C, 58·1; H, 5·0; N, 11·5. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·8; N, 11·3%). After melting, the substance solidified to a yellowish-brown mass which then had m. p. *ca.* 270—275°. The yield of hydrazide was diminished when the reaction mixture was heated.

The following derivatives were prepared by warming the acylhydrazide with the carbonyl compound in alcoholic solution in presence of a trace of acetic acid, and, if necessary, dilution with water, and crystallisation from alcohol except where otherwise stated: *benzylidene*, fine needles, m. p. 264° (Found: C, 68·1; H, 4·8; N, 8·1. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3%); *isopropylidene*, fine needles (from dilute alcohol), m. p. 209° (Found: C, 62·3; H, 5·5; N, 9·6. $C_{15}H_{18}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%); *ethylidene*, glistening plates, m. p. 194° (Found: C, 61·5; H, 5·2; N, 10·0. $C_{14}H_{14}O_4N_2$ requires C, 61·3; H, 5·1; N, 10·2%); *methylene*, fine prismatic needles, m. p. 156° (Found: C, 59·8; H, 4·8; N, 11·0. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·8%). *7-Methoxycoumarin-4-acethydrazones* were also prepared from: acetophenone, small prisms, m. p. 215° (Found: C, 66·3; H, 5·1; N, 7·9. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1; N, 8·0%); methyl ethyl ketone, fine needles (from dilute alcohol), m. p. 176° (Found: C, 63·4; H, 5·9; N, 9·4. $C_{16}H_{20}O_4N_2$ requires C, 63·6; H, 6·0; N, 9·3%); pyruvic acid (boiled under reflux for ½ hour), prisms (from dilute alcohol), m. p. 220° (Found: C, 56·3; H, 4·6; N, 8·5. $C_{14}H_{14}O_6N_2$ requires C, 56·6; H, 4·4; N, 8·8%); dihydro-orcinol (1 : 3-diketo-5-methyl-*cyclo*hexane) (boiled under reflux for ½ hour), faintly yellow needles (from dilute alcohol), m. p. 258° (decomp.) (Found: C, 64·0; H, 5·9; N, 9·2. $C_{19}H_{20}O_4N_2$ requires C, 64·0; H, 5·6; N, 7·9%).

Analyses are by Drs. Weiler and Strauss, Oxford, and by Mrs. W. M. Eno, Bristol.

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38. *Synthetic Long-chain Aliphatic Compounds. Part I. Introduction. Myristic, Stearic, and Tricosanoic Acids.*

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As a start in the systematic synthesis of long-chain, saturated and unsaturated acids, myristic, stearic, and ω-tricosanoic acids have been prepared from the corresponding keto-acids by the ketone synthesis devised by Bowman (*J.*, in the press). A convenient method for the preparation of ω-bromoheptoic acid on a large scale has been devised.

Previous methods of synthesis of long-chain fatty acids may conveniently be classified into those using a β-keto-ester as intermediate and those using organo-metallic compounds. The most important of the first group is the well-known Robinson–Robinson synthesis (*J.*, 1925, **127**, 175; 1930, 745) in which an acylacetoacetic ester is submitted to graded hydrolysis to yield the keto-acid:

$$R\cdot CO\cdot \underset{CO_2Et}{\overset{CO\cdot CH_3}{C}}\cdot X\cdot CO_2Et \longrightarrow R\cdot CO\cdot CH_2\cdot X\cdot CO_2H + CH_3\cdot CO_2H$$

Though this synthesis gives good results in some cases it often suffers from the disadvantage of low yields and occasionally the separation of the products is difficult. This may be caused by hydrolysis in two directions with partial elimination of the "wrong" acyl group.

The second group, *viz.*, methods involving organo-metallic reagents, has been much used in recent years:

$$R_2M + Cl\cdot CO\cdot [CH_2]_n\cdot CO_2Et \longrightarrow R\cdot CO\cdot [CH_2]_n\cdot CO_2Et$$

The most important of these reagents are the cadmium dialkyls (Cason, *Chem. Reviews*, 1947, **40**, 15) although the zinc alkyls have been shown to give excellent yields of keto-acids containing up to thirty-five carbon atoms (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2350). The dialkylcadmium synthesis is probably the most convenient method for the preparation of straight-chain keto-acids up to C_{31} when the "chain-extender," *i.e.*, the acid chloride ester, is readily available and R is not too large. The disadvantages of this method are the difficulty of preparing the "chain-extender" (cf. Drake and Melamed, *J. Amer. Chem. Soc.*, 1948, **70**, 364) and the well-known tendency of the Wurtz reaction to become appreciable when Grignard reagents are prepared from the higher alkyl halides, with, often, difficulty in separating the resultant saturated paraffin R–R from the product (*inter al.*, Houston, *J. Amer. Chem. Soc.*, 1947, **69**, 517).

The new ketone synthesis described recently (*J.*, in the press) appears to be particularly well suited for the synthesis of long-chain aliphatic compounds. As applied to saturated fatty acids, it may be represented as follows:

$$\underset{(I.)}{(EtO_2C)_2CH\cdot[CH_2]_n\cdot CO_2Et} \xrightarrow[\text{EtOH}]{\text{Na-}} \underset{(II.)}{(CH_2Ph\cdot O_2C)_2CNa\cdot[CH_2]_n\cdot CO_2\cdot CH_2Ph} \xrightarrow{R\cdot COCl\ (III.)}$$

$$\underset{(IV.)}{(CH_2Ph\cdot O_2C)_2\overset{CO\cdot R}{C}\cdot[CH_2]_n\cdot CO_2\cdot CH_2Ph} \xrightarrow[Pd\text{-}C]{H_2} \underset{(V.)}{(HO_2C)_2\overset{CO\cdot R}{C}\cdot[CH_2]_n\cdot CO_2H} \longrightarrow$$

$$\underset{(VI.)}{R\cdot CO\cdot[CH_2]_{n+1}\cdot CO_2H} \longrightarrow \underset{(VII.)}{R\cdot[CH_2]_{n+2}\cdot CO_2H}$$

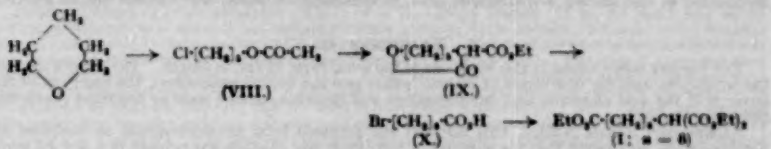
The advantages of the debenzylation synthesis are several. First, the yields are usually 70% or higher; secondly, the "chain-extender" is a malonic ester which may be obtained in several ways and may be purified through the crystalline triacid (cf. the β-keto-ester synthesis); thirdly, the intermediate reactant (IV) is rendered soluble by the three benzyl groups, so that subsequent reactions can be carried out in not too dilute solution.

One of the aims, therefore, of the present series of papers is to utilise this reaction for the preparation of fatty compounds of greater chain lengths than has hitherto been possible. Parallel researches are in hand on the synthesis of the higher unsaturated acids using the procedure already described in a preliminary note (Bowman, *Nature*, 1949, **163**, 95).

Before proceeding with the main objective we have examined two further applications of this synthesis and obtained thereby myristic and stearic acids.

For the synthesis of the former we chose the route employing hexanoyl chloride (III; R = C_5H_{11}) and ethyl heptane-1 : 1 : 7-tricarboxylate (I; $n = 6$). The latter has been previously

obtained, in poor yield, by thermal degradation of the corresponding oxalo-ester obtained from ethyl azelaate (Zakutskaya and Gudovich, *J. Gen. Chem., Russia*, 1938, **8**, 216). Since it was required in considerable quantity for another investigation, we have examined a number of routes for its preparation and have developed a method based on tetrahydropyran which makes ω-bromoheptanoic acid readily accessible.



(VIII.) (IX.)

$$Br\cdot[CH_2]_6\cdot CO_2H \longrightarrow EtO_2C\cdot[CH_2]_6\cdot CH(CO_2Et)_2$$
(X.) (I; $n = 6$)

Tetrahydropyran was converted into δ-chloroamyl acetate (VIII) by acetyl chloride in the presence of zinc chloride (Synerholm, *J. Amer. Chem. Soc.*, 1947, **69**, 2581), and the chloro-ester treated with sodiomalonic ester in alcohol to give the lactone ester (IX). Hydrobromic–acetic acids, followed by hydrobromic–sulphuric acids (Brown and Partridge, *J. Amer. Chem. Soc.*, 1944, **66**, 839), then furnished 7-bromoheptanoic acid • (X) in 60% overall yield. Finally the bromo-acid was azeotropically esterified in almost quantitative yield and treated with sodiomalonic ester in the usual manner to give the required triester (I; $n = 6$). Conversion of this into the corresponding tribenzyl sodio-ester and reaction of this material with *n*-hexanoyl chloride afforded a keto-ester (IV; $R = C_5H_{11}$; $n = 6$) which was debenzylated and decarboxylated to give *9-ketotetradecanoic acid* • (VI; $R = C_5H_{11}$; $n = 6$). Wolff–Kishner reduction at atmospheric pressure (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) then furnished myristic acid.

An alternative keto-acid synthesis would utilise the reaction of an acid chloride ester with a benzyl alkylsodiomalonate, thus:

$$\underset{\text{(XI.)}}{EtO_2C\cdot[CH_2]_n\cdot COCl} + Na\cdot CR(CO_2\cdot CH_2Ph)_2 \longrightarrow \underset{\text{(XIII.)}}{(CH_2Ph\cdot O_2C)_2CR\cdot CO\cdot[CH_2]_n\cdot CO_2Et}$$
(XII.)

$$\xrightarrow[Pd\text{-}C]{H_2} R\cdot CH_2\cdot CO\cdot[CH_2]_n\cdot CO_2H \longrightarrow \underset{\text{(XV.)}}{R\cdot[CH_2]_{n+1}\cdot CO_2H}$$
(XIV.)

Accordingly, to test this route, sebacic ester chloride (XI; $n = 8$) was condensed with benzyl *n*-heptylsodiomalonate (XII; $R = C_7H_{15}$) and the resulting keto-triester (XIII; $R = C_7H_{15}$, $n = 8$) submitted to the usual reactions to give the known 10-keto-octadecanoic acid (XIV; $R = C_7H_{15}$, $n = 8$), which was then reduced to stearic acid.

Our main objective being to ascend the fatty acids series as rapidly as possible, it will be necessary to prepare "chain-extenders" of the general formula (I) where n is as great as possible. Aliphatic ωω-dicarboxylic esters are available by a number of routes and accordingly we have examined methods for their conversion into the corresponding malonic esters (I). The carbethoxylation technique of Wallingford *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 2056) using ethyl carbonate appeared to be of interest since it is a one-stage process and has already been applied to sebacic ester (XVI; $n = 7$) by the same authors, to give a product formulated by them as

$$\underset{\text{(XVI.)}}{EtO_2C\cdot[CH_2]_n\cdot CH_2\cdot CO_2Et} \xrightarrow[NaOEt]{Et_2CO_3} \underset{\text{(XVII.)}}{EtO_2C\cdot[CH_2]_n\cdot CH(CO_2Et)_2}$$

(XVII; $n = 7$). In our hands, however, this product, although similar, was impure as shown by a low saponification value and a wide boiling range; and the derived tricarboxylic acid had neither the required equivalent weight nor a sharp melting point. We therefore abandoned this method and investigated an alternative route by way of the oxalo-ester (XVIII).

$$\text{(XVI)} \xrightarrow{Et_2C_2O_4} \underset{\text{(XVIII.)}}{EtO_2C\cdot[CH_2]_n\cdot CH(CO_2Et)(CO\cdot CO_2Et)} \xrightarrow{-CO} \text{(XVII)}$$

After some preliminary experiments we obtained the required ethyl *n*-octane-1 : 1 : 8-tricarboxylate (XVII; $n = 7$) in good yield and in a high state of purity from ethyl sebacate,

• Geneva numbering is used in this series of papers.—Ed.

without purification of the intermediate oxalo-ester (XVIII; $n = 7$) (cf. Zakutskaya, *J. Gen. Chem., Russia*, 1940, **10**, 1553). Myristoyl chloride was condensed with benzyl sodio-octane-1 : 1 : 8-tricarboxylate (II; $n = 7$), and the resulting keto-triester (IV; $R = C_{13}H_{27}$; $n = 7$) was debenzylated and decarboxylated by the general method. 10-*Ketotricosanoic acid* (VI; $R = C_{13}H_{27}$; $n = 7$) was thus obtained in exceptionally high yield (crude, 93%; pure, 85%). Reduction to the known *n*-tricosanoic acid, in quantitative yield, was carried out as above.

Experimental.

The Vigreux column used in this work was of the usual type, 22 cm. in length. The Fenske column, the techniques used for conversion of malonic esters into the benzyl sodio-esters, the reactions of the latter with the acid chlorides, and debenzylations and decarboxylations were as described previously (Bowman, *loc. cit.*).

δ-Chloroamyl Acetate (VIII).—This material was prepared from tetrahydropyran as described by Synerholm (*loc. cit.*) except that the quantity of anhydrous zinc chloride was reduced (5 g. per 2·5 mols. of acetyl chloride) and the product was distilled directly from the reaction mixture through the Vigreux column.

7-Bromoheptanoic Acid (X).—The foregoing chloro-compound (434 g., 2·63 mols.) was treated with sodiomalonic ester (3·2 mols.) in absolute ethanol (500 ml.) in the presence of sodium iodide (20 g.) at 110° for 6 hours. After removal of most of the ethanol and ethyl acetate by distillation, the cooled reaction mixture was added to dilute sulphuric acid, and the product, after saturation of the aqueous layer with ammonium sulphate, isolated with benzene (2 × 400 ml.). The solvent-free oil thus obtained was mixed with glacial acetic acid (500 ml.) and constant-boiling hydrobromic acid (500 ml.), and the resulting mixture slowly distilled through a Vigreux column, ethyl acetate (400 ml.) containing some ethyl bromide being collected during 4 hours; during this last phase decarboxylation had already started and was completed by further refluxing for 1 hour after the addition of sulphuric acid (50 ml.; 20%). The cooled solution was then mixed with a further portion of constant-boiling hydrobromic acid (500 ml.) and concentrated sulphuric acid (150 ml.), and the mass heated at 110° (internal temperature) for 4 hours. After cooling to room temperature, the reaction mass was diluted with water, and the lower layer of bromo-acid separated; further product was obtained by extraction of the aqueous layer, previously saturated with ammonium sulphate, with ether (3 × 400 ml.). The combined organic extracts were then washed with water, dried (Na_2SO_4), and treated with active charcoal to remove most of the colour, and the solvent removed by distillation. The residue was found to contain some water and, accordingly, was mixed with benzene (1 l.), and the mixture refluxed with a phase-separator (Dean and Stark) until dry. After removal of solvent and a small fore-run, 7-bromoheptanoic acid was obtained as an almost colourless oil, b. p. 140—142°/1·5 mm. (378 g.; 60%, calc. on the tetrahydropyran), which solidified and had m. p. 28—29° (thermometer in liquid). The bromo-acid was characterised by conversion in the usual manner into the corresponding phenoxy-acid which separated from light petroleum (b. p. 40—60°) in needles, m. p. 56° (von Braun, *Ber.*, 1906, **39**, 4362, gave m. p. 56—57°).

Ethyl 7-Bromoheptanoate.—A mixture of the bromo-acid (376 g.), benzene (700 ml.), ethanol (300 ml.) and AnalaR concentrated sulphuric acid (3 ml.) was distilled through the Fenske column fitted with a phase-separator until no further phase-separation took place. The cooled solution was washed with water, sodium hydrogen carbonate solution, and again water, dried (Na_2SO_4), and distilled to give, after rejection of a fore-run (10 g.), the ethyl ester as a colourless liquid, b. p. 112°/5 mm., n_D^{20} 1·4608 (397 g., 93%).

Ethyl n-Heptane-1 : 1 : 7-tricarboxylate (I; $n = 6$).—The foregoing ester (237 g.; 1 mol.) was treated with sodiomalonic ester (1·75 mols.) in dry ethanol (700 ml.) in the presence of sodium iodide (10 g.) at 90—105° for 10 hours. After removal of solvent by distillation, the cooled mixture was treated with excess of dilute sulphuric acid and isolated in the usual manner to give the triester as a colourless oil, b. p. 146—147°/0·5 mm., n_D^{20} 1·4411 (263 g., 83%).

9-Ketotetradecanoic Acid (VI; $R = C_9H_{11}$; $n = 6$).—Ethyl *n*-heptane-1 : 1 : 7-tricarboxylate (31·6 g., 0·1 mol.) was converted into the corresponding tribenzyl sodio-ester by means of sodium (2·3 g., 0·1 mol.), benzyl alcohol (32·5 g., 0·3 mol.) in benzene (300 ml.), and the product treated with hexanoyl chloride (b. p. 94°/120 mm.; 13·5 g., 0·1 mol.) according to the general procedure. The product was hydrogenated in ethanol (160 ml.) containing ethyl acetate (20 ml.), palladised charcoal (5 g.; 10%), and palladised strontium carbonate (5 g. of 10%). The catalyst was removed by filtration, the filtrate refluxed for 0·5 hour to bring about decarboxylation, and the solvent removed at atmospheric pressure and finally *in vacuo*. The residue was boiled with acetic acid (75 ml.) containing sulphuric acid (2·5 ml. of 20%) for 0·5 hour to bring about ketone hydrolysis of any residual β-keto-ester, and the product was isolated by dilution with water and filtration; yield, 17 g. (70%); m. p. 59—61°. On crystallisation from light petroleum (b. p. 40—60°) *9-ketotetradecanoic acid* separated in rosettes of needles, m. p. 66° (Found: C, 69·4; H, 10·7. $C_{14}H_{26}O_3$ requires C, 69·4; H, 10·7%). The *p-bromophenacyl* ester crystallised from 96% ethanol (norite) in needles, m. p. 78° (Found: C, 60·7; H, 6·9. $C_{30}H_{41}O_4Br$ requires C, 60·1; H, 7·3%).

A sample of the keto-acid was reduced with hydrazine and sodium hydroxide in 2 : 2′-dihydroxydiethyl ether, following exactly the procedure of Huang-Minlon (*loc. cit.*), to give myristic acid (80%) which separated from light petroleum (b. p. 40—60°) at −20° in plates, m. p. 53·5—54° (capillary) undepressed by admixture with authentic material.

10-Keto-octadecanoic Acid (XIV; $R = C_{13}H_{27}$; $n = 8$).—*n*-Heptylmalonic ester (b. p. 118—119°/1·5 mm.; 18·1 g., 0·07 mol.) was converted by sodium (1·61 g., 0·07 mol.) in benzene (300 ml.) into the sodium salt of its enolic form and treated with benzyl alcohol (15·5 g., 0·14 mol.) in the usual manner, to give benzyl sodio-*n*-heptylmalonate. This was then treated with sebacic ethyl ester chloride (17·4 g., 0·07 mol.), and the product debenzylated and decarboxylated as usual to give the crude product

which was hydrolysed and isolated as in the previous experiment. The mixed acids, so obtained, were converted into their ethyl esters by azeotropic esterification and unchanged materials removed by distillation up to 190° (bath)/1 mm. The residual crude ethyl ester was hydrolysed with alkali and the keto-acid obtained in the usual manner, collected, and dried; yield, 14·9 g. (71%); m. p. 79—82°. 10-Keto-octadecanoic acid crystallised from light petroleum (b. p. 80—100°) in plates, m. p. 83°, and was characterised by conversion into the oily oxime and thence into the derived amide, plates (from methanol), m. p. 80° (cf. Robinson and Robinson, *J.*, 1926, 2207).

Ethyl n-*Octane*-1 : 1 : 8-*tricarboxylate* (XVII; $n = 7$).—Ethyl oxalate (73 g., 0·5 mol.) was added to a stirred suspension of ethanol-free sodium ethoxide (from 11·5 g. of sodium; 0·5 mol.) in dry benzene (400 ml.), followed by ethyl sebacate (XVI) (161 g., 0·62 mol.). The resulting homogeneous solution was kept at room temperature for 24 hours and extracted with ice-water (1 l.). The organic layer was then extracted with aqueous sodium hydroxide (1 l.; 0·5N.) at 0°, and the combined aqueous extracts were washed with fresh benzene (200 ml.). Acidification of the combined aqueous extracts was effected in the presence of benzene (200 ml.) and ice with hydrochloric acid (250 ml.; 5N.). After the washing with water, the benzene solution was evaporated to dryness *in vacuo*, to give the crude oxalo-ester (XVIII; $n = 7$) (126 g.). The combined benzene extracts of neutral materials furnished, on distillation and fractionation, recovered ethyl sebacate (66 g.).

The crude oxalo-ester was heated at 160—180°/5 mm. in the presence of powdered glass for 3 hours, whereafter no further gas evolution took place. Distillation of the residue through a fractionating column (15 × 1·2 cm. containing 3-mm. Fenske helices) furnished ethyl n-octane-1 : 1 : 8-tricarboxylate as a colourless oil, b. p. 160°/1 mm., n_D^{20} 1·4436, d_4^{20} 1·015 (Found: C, 61·6; H, 9·0; sap. val., 110. Calc. for $C_{17}H_{28}O_6$: C, 61·8; H, 9·1%; sap. equiv., 110). The yield of this material was 88 g. (72% based on unrecovered ethyl sebacate). Lower- (sap. equiv., 120) and higher-boiling fractions (sap. val., 105) were rejected.

A sample of the triester was hydrolysed with aqueous-alcoholic sodium hydroxide, and the n-*octane*-1 : 1 : 8-*tricarboxylic acid*, obtained by addition of *excess* of sulphuric acid, crystallised from ethylene dichloride–ethyl acetate whence it separated in rosettes of colourless needles, m. p. 108—109° (Found: C, 53·0; H, 6·9; equiv., 82. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3%; equiv., 82). On heating at 160—180° it was converted into sebacic acid, leaflets (from water), m. p. and mixed m. p. 133°.

10-*Ketotricosanoic Acid* (VI; $R = C_{15}H_{31}$; $n = 7$).—Benzyl sodio-n-octane-1 : 1 : 8-tricarboxylate (0·1 mol.) was prepared in the usual manner from the foregoing triester (33·0 g., 0·1 mol.), sodium (2·3 g., 0·1 mol.), and benzyl alcohol (33·4 g., 0·3 mol.) in benzene solution and treated with myristoyl chloride [24·65 g., 0·1 mol.; b. p. 134°/2·5 mm. from acid, m. p. 53·6° (thermometer in liquid)]. The next stages, *i.e.*, hydrogenation, decarboxylation, and working up were carried out as for 9-ketotetradecanoic acid. The yield of crude material, m. p. 86°, was 36·2 g. (93%). The product contained some ester and was hydrolysed. Thus, 10·0 g. of crude acid were boiled with sodium hydroxide (100 ml.; N.) for 1 hour and acidified at the b. p., with shaking. 10-*Ketotricosanoic acid* was crystallised once from benzene (30 ml.) and then twice from acetone (100 ml. each time), from which it (5·7 g.) separated in colourless plates, m. p. 93·5° (constant) (Found: C, 74·7; H, 11·9. $C_{36}H_{44}O_3$ requires C, 75·0; H, 11·9%). The solubility of the keto-acid in acetone at 15° is *ca.* 0·2 g. per 100 ml.

It formed an *oxime* which crystallised from light petroleum (b. p. 40—60°) at 0° in plates, m. p. 43° (Found: N, 3·55. $C_{24}H_{41}O_2N$ requires N, 3·65%).

n-*Tricosanoic Acid*.—The foregoing keto-acid (20·2 g.) was reduced in the same manner as before using 2 : 2′-dihydroxydiethyl ether (150 ml.), hydrazine hydrate (14 ml.; 50%), and potassium hydroxide (12 g.) under reflux for 1·5 hours and then at 195° for 6 hours. The acid (19·4 g.; 100%) had m. p. 79° and was practically pure. It was crystallised from benzene (50 ml.) to give material, m. p. 79·1°, and then twice from acetone (70 ml., each time) from which it separated in colourless plates (17·9 g., m. p. 79·2° (constant). The solubility of n-tricosanoic acid in benzene at 15° is *ca.* 0·5 g. per 100 ml. and in acetone at 15° *ca.* 1 g. per 100 ml.

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39. *Synthetic Long-chain Aliphatic Compounds. Part II. Erucic and Brassidic Acids. A New Olefin Synthesis.*

By R. E. BOWMAN.

A new olefin synthesis, whereby methoxy-ketones (IV) are converted into the corresponding methoxy-alcohols (V) and thence, by successive treatment with hydrogen bromide and zinc, into the olefin (VI), has led to the total synthesis of erucic and brassidic acids (for a preliminary account of this work, see *Nature*, 1949, **163**, 95).

CONCURRENTLY with the synthesis of saturated acids (Part I, preceding paper), we were interested in developing a new and general method of synthesis of the corresponding unsaturated compounds, particularly since, at the time when these experiments were begun, the only general syntheses of olefinic acids (Noller and Bannerot, *J. Amer. Chem. Soc.*, 1934, **56**, 1563) were based on the method of Boord (*ibid.*, 1930, **52**, 3396). This synthesis, however, suffers from the disadvantage that the starting materials, ω-chloro-aldehydes, are difficult of access, although

a later modification due to Baudart (*Compt. rend.*, 1943, **217**, 399; 1945, **220**, 404) has, to some extent, eased this situation.

Ruzicka, Plattner, and Widmer (*Helv. Chim. Acta*, 1942, **25**, 604, 1086) have recently developed a new method employing a symmetrical acyloin as intermediate. This method has since been modified by Baudart (*Bull. Soc. chim.*, 1946, [v], **13**, 87) to allow of the synthesis of the asymmetrical monobasic unsaturated acids. When this work was nearing completion, Ahmad and Strong (*J. Amer. Chem. Soc.*, 1948, **70**, 1699) reported a new general method based on the semi-hydrogenation of the corresponding acetylenic acid (cf. Bhattacharya, Saletore, and Simonsen, *J.*, 1928, 2678).

Two routes, both employing our new ketone synthesis (*J.*, in the press), were available, one using the acyloin $R{\cdot}CH(OH){\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2H$ and starting from the appropriate α-acetyl-acid chloride, the other using the α-alkoxy-acid chloride (I) and the α-alkoxy-ketone (IV) in the following general manner:

$$\underset{\text{(I.)}}{CH_3O{\cdot}CHR{\cdot}COCl} + \underset{\text{(II.)}}{(CH_2Ph{\cdot}O_2C)_3CNa{\cdot}X{\cdot}CO_2{\cdot}CH_2Ph} \longrightarrow \underset{\text{(III.)}}{(CH_2Ph{\cdot}O_2C)_3C{\cdot}X{\cdot}CO_2{\cdot}CH_2Ph}$$

$$\xrightarrow[\text{(ii) } -2CO_2]{\text{(a) } H_2\text{-Pd-C}} \underset{\text{(IV.)}}{CH_3O{\cdot}CHR{\cdot}CO{\cdot}CH_2{\cdot}X{\cdot}CO_2H} \longrightarrow \underset{\text{(V.)}}{CH_3O{\cdot}CHR{\cdot}CH(OH){\cdot}CH_2{\cdot}X{\cdot}CO_2H}$$

$$\longrightarrow R{\cdot}CHBr{\cdot}CHBr{\cdot}CH_2{\cdot}X{\cdot}CO_2H \longrightarrow \underset{\text{(VI.)}}{R{\cdot}CH{:}CH{\cdot}CH_2{\cdot}X{\cdot}CO_2H}$$

The experiments now described herein had as their objective the realisation of the second route as applied to the synthesis of erucic and brassidic acids (VI; $R = C_9H_{17}$, $X = [CH_2]_{10}$).

The early experiments were concerned with the preparation of 2-methoxydecanoic acid * from the corresponding methyl bromo-ester by treatment with methanolic sodium methoxide.

$$CH_3R{\cdot}CO_2H \longrightarrow Br{\cdot}CHR{\cdot}CO_2CH_3 \longrightarrow CH_3O{\cdot}CHR{\cdot}CO_2CH_3 \longrightarrow CH_3O{\cdot}CHR{\cdot}CO_2H$$

Considerable difficulty was encountered in obtaining the α-methoxy-acid free from a small amount of impurity, but eventually by careful fractionation of the crude methyl 2-methoxydecanoate through a Fenske column, the pure *ester* was obtained and thence, by hydrolysis, pure *2-methoxydecanoic acid*. The acid was converted into the corresponding chloride (I; $R = C_8H_{17}$) with thionyl chloride without rearrangement (as shown by its hydrolysis by dilute alkali to give the original acid in a pure state). Condensation with tribenzyl sodioundecane-1 : 1 : 11-tricarboxylate (II; $X = [CH_2]_{10}$) furnished the keto-ester which, on hydrogenolysis and decarboxylation according to the general method, yielded *13-keto-14-methoxydocosanoic acid* (IV; $R = C_8H_{17}$, $X = [CH_2]_{10}$) as a low-melting solid.

Before proceeding with the olefin synthesis, the action of a number of reducing agents on this methoxy-ketone was examined. Sodium and ethanol furnished an oil and a small amount of a crystalline solid, m. p. 87—87·5°, which is formulated as *13-hydroxydocosanoic acid* (VII)

$$\underset{\text{(VIII.)}}{C_8H_{17}{\cdot}\overset{OH}{\overset{|}{C}}H{\cdot}[CH_2]_{10}{\cdot}CO_2H} \xleftarrow[\text{etc.}]{Zn} C_8H_{17}{\cdot}\overset{OCH_3}{\overset{|}{C}}H{\cdot}CO{\cdot}[CH_2]_{11}{\cdot}CO_2H \xrightarrow{H} \underset{\text{(VII.)}}{C_8H_{17}{\cdot}CH_2{\cdot}\overset{OH}{\overset{|}{C}}H{\cdot}[CH_2]_{11}{\cdot}CO_2H} + CH_3{\cdot}OH$$

[cf. the reduction of ethoxyacetone by sodium amalgam and acid to give acetone and ethanol (Fittig and Erlenbach, *Annalen*, 1892, **269**, 22), and a similar reduction of an acyloin by sodium and ethanol to give some of the corresponding monohydroxy-compound (Ruzicka *et al.*, *loc. cit.*)]. Reductions with zinc and acid under a variety of conditions gave rise, in high yield, to an isomeric hydroxy-acid, m. p. 90°, depressed to 78—82° by admixture with the previous product, and formulated as *14-hydroxydocosanoic acid* (VIII.). A sample of this material was oxidised to the corresponding keto-acid, m. p. 85° (lit., 85°) which raised the m. p. of a sample of 14-ketodocosanoic acid, m. p. 83°, obtained previously by the hydration of behenolic acid with sulphuric acid (Holt and Baruch, *Ber.*, 1893, **26**, 838), a reaction unlikely to result in unidirectional addition (Robinson and Robinson, *J.*, 1925, **127**, 175; 1930, 745).

Attempts to reduce the methoxy-ketone catalytically with Adams's catalyst were not successful. Reduction with aluminium *iso*propoxide, however, furnished a solid product which was separated by light petroleum into a solid *13-hydroxy-14-methoxydocosanoic acid* (V; $R = C_8H_{17}$, $X = [CH_2]_{10}$) and a liquid product containing some unchanged methoxy-acid. The liquid fraction, on treatment with hydrogen bromide followed by zinc dust in alcohol, gave a

* Geneva nomenclature is used in this paper.—Ed.

solid from which brassidic and erucic acids were isolated. Both acids were obtained pure and shown to be identical with materials obtained from natural sources, by mixed melting points of the parent acids, their *p*-bromophenacyl esters, and the derived dihydroxy-acids obtained by the action of peracetic acid (Dorée and Pepper, *J.*, 1942, 477).

Conversion of the solid hydroxy-methoxy-acid into the dibromide proved more difficult. We were, at that time, unaware of Baudart's technique (*loc. cit.*) which has since been used with success, but finally by treatment with gaseous hydrogen bromide at 150—160° for 6 hours followed by zinc dust, a moderate yield of brassidic acid was obtained.

It is realised that the method for conversion of the hydroxy-methoxy-acids into the olefinic acid used in this work is far from satisfactory. Experiments are in hand on the development of a technique suitable for general application and will be reported later.

Experimental.

The equipment and techniques employed were as described in Part I.

Decanoic Acid.—A sample of commercial ethyl decanoate (Messrs. A. Boake, Roberts & Co., Ltd.) was fractionated through the Fenske column (total-reflux head) and the fraction, b. p. 118°/10 mm., collected. The acid obtained by hydrolysis was distilled (Vigreux column) and the fraction, b. p. 118—119°/1·5 mm., m. p. 31° (thermometer in liquid), was used.

Methyl 2-Bromodecanoate.—Decanoic acid (110 g.) was converted into its chloride with thionyl chloride (75 ml.). After removal of excess of the latter *in vacuo*, the mass was heated to 110° and treated with bromine (40 ml.) in the usual manner and finally poured into methanol (300 ml.) and left overnight. Isolated as usual the ester was distilled through a column (Vigreux), and the fraction (140 g.), b. p. 89°/0·5 mm., collected.

2-Methoxydecanoic Acid.—The foregoing ester was added with stirring to a solution of sodium methoxide (from 17 g. of metal) in methanol (300 ml.; magnesium-dried), and the mixture boiled under reflux for 4 hours, whereafter most of the solvent was removed by distillation. The cooled residue was diluted with water, and the product isolated with light petroleum (b. p. 40—60°). The oil thus obtained was treated with a mixture of silver oxide (10 g.) and methyl iodide (15 ml.) in acetone solution (100 ml.) under reflux for 6 hours. After removal of solid material by filtration, the product was carefully distilled through the Fenske column to give fractions, (i) b. p. 86—97°/12 mm. (15 ml.) and (ii) pure *methyl 2-methoxydecanoate*, b. p. 97°/2 mm., n_D^{20} 1·4312 (70 g.) (Found: C, 66·7; H, 10·9. $C_{11}H_{22}O_3$ requires C, 66·7; H, 11·1%).

The ester (70 g.) was hydrolysed by treatment with sodium hydroxide (50 ml. of 10*N*.) in methanol (70 ml.) for ½ hour, dilution with water (300 ml.), and boiling with escape of methanol (1 hour). Acidification of the cooled solution with sulphuric acid (50 ml. of 20*N*.) furnished the acid which was isolated with light petroleum (b. p. 40—60°). *2-Methoxydecanoic acid* was obtained as a colourless oil, b. p. 118°/0·5 mm., which solidified immediately and then had m. p. 42·5° (thermometer in liquid). A sample crystallised from light petroleum (b. p. 40—60°) at −10° in colourless slender needles, m. p. 43—43·5° (capillary) (Found: C, 65·5; H, 10·7. $C_{11}H_{22}O_3$ requires C, 65·34; H, 10·9%). It was characterised as the *tribromoanilide*: the acid chloride (see below; 1·7 g.) was added to a solution of tribromoaniline (2 g.) and pure dimethylaniline (2 g.) in dry, purified dioxan (10 ml.), and the mixture refluxed for 0·5 hour; the cooled solution was poured into excess of dilute hydrochloric acid, and the solid removed by filtration; after being washed with water and triturated with alkali and then with water, the product crystallised from aqueous alcohol (norite) in rosettes of slender needles, m. p. 81—82° (Found: C, 39·8; H, 4·7. $C_{17}H_{24}O_2NBr_3$ requires C, 39·7; H, 4·8%).

2-Methoxydecanoyl Chloride (I; R = C_8H_{17}).—A mixture of the foregoing acid (61 g.) and purified thionyl chloride (50 ml.) was kept successively at room temperature for 1 hour, at 30° for 2 hours, and finally at 60° for the same period. Distillation gave the *acid chloride* as a colourless liquid with a characteristic odour and b. p. 83—84°/0·4 mm. (62 g., 93%). It was characterised as the tribromoanilide (as above) and by mild hydrolysis at room temperature with aqueous sodium hydrogen carbonate whence acidification at 0° gave the original acid, m. p. 42° (air-dried) undepressed by admixture with the original material.

Ethyl ω-Bromoundecanoate.—The bromo-acid (Ashton and Smith, *J.*, 1934, 438; m. p. 51°) was esterified azeotropically in the manner described for the corresponding bromoheptoic acid in Part I (*loc. cit.*). The ester was thus obtained as a colourless oil (98%), b. p. 118—119°/0·15 mm.

Ethyl n-*Undecane*-1 : 1 : 11-*tricarboxylate.*—The above bromo-ester (154 g., 0·53 mol.) was treated with sodiomalonic ester (0·75 mol.) in absolute ethanol (300 ml.) under reflux for 6 hours. Isolated in the usual manner, the triester was carefully distilled and, after rejection of a fore-run (b. p. 80—180°), was collected at 180—182°/0·15 mm., m. p. 0—1° (150 g., 76%).

13-Keto-14-methoxydocosanoic Acid (IV; R = C_8H_{17}, X = $[CH_2]_{10}$).—The foregoing triethyl ester (93 g., 0·25 mol.) was converted into the sodium salt of its enol in benzene (300 ml.) with powdered sodium (5·75 g., 0·25 mol.) and treated with benzyl alcohol (81 g., 0·75 mol.) according to the general procedure to give the corresponding tribenzyl sodio-ester (II; X = $[CH_2]_{10}$). The latter was treated with 2-methoxydecanoyl chloride (55 g., 0·25 mol.), and the product in ethanol (200 ml.) containing ethyl acetate (100 ml.) was debenzylated and decarboxylated as usual. The residue obtained after removal of solvent was treated with light petroleum (b. p. 40—60°; 500 ml.) at 0° and filtered from solid material. Solvent and unchanged 2-methoxydecanoic acid were removed by distillation up to 200° (bath temperature) at 0·2 mm. pressure to give the crude *keto-methoxy-acid* (68 g., 71%) which solidified at room temperature and was used directly for future experiments. A sample was crystallised from light petroleum (b. p. 40—60°) at −25° and furnished the pure acid in colourless plates, m. p. 32—33° (Found: C, 71·2; H, 11·2. $C_{23}H_{44}O_4$ requires C, 71·9; H, 11·4%).

Reduction Experiments.—Sodium and ethanol. The crude keto-methoxy-acid (2 g.) was dissolved in boiling ethanol (25 ml.) and treated with sodium (2 g.) in portions. Dilution with water and acidification afforded a gummy product which was dissolved in boiling methanol (15 ml.). On cooling, 13-*hydroxydocosanoic acid* (0·4 g.), m. p. 86—87°, separated. It crystallised from ethyl acetate in tiny colourless prisms, m. p. 87—87·5° (Found: C, 74·3; H, 11·9. $C_{22}H_{44}O_3$ requires C, 74·2; H, 12·3%).

Zinc. The keto-methoxy-acid (2 g.) was submitted to the following procedures. (*a*) Clemmensen reduction with amalgamated zinc (15 g.) in hydrochloric acid (5N.) for 6 hours. (*b*) Refluxing with zinc dust (12 g.) in 70% acetic acid containing hydrochloric acid (3 drops of 10N.) for 0·5 hour. (*c*) Its solution in ethanol (40 ml.) mixed with amalgamated zinc dust (10 g.) with periodic addition of hydrochloric acid (20 ml. of 10N.) over 2 hours, the temperature being kept below 15°, and finally, hydrolysis of the crude product with alkali. In all cases, a high yield (90%) of 14-*hydroxydocosanoic acid* was obtained. Crystallisation from acetone furnished the hydroxy-acid in colourless prisms, m. p. 90°, depressed to 78—82° by admixture with the 13-isomer (Found: C, 73·9; H, 12·5. $C_{22}H_{44}O_3$ requires C, 74·2; H, 12·3%).

A sample was oxidised in warm acetic acid solution with chromic acid (20N.) to give the 14-ketodocosanoic acid which separated from aqueous alcohol in plates, m. p. 85°. A mixture of this keto-acid and a sample of 14-ketodocosanoic acid, m. p. 83° (prepared from behenolic acid and sulphuric acid), melted at 83—84°.

Aluminium isopropoxide. The crude keto-methoxy-acid (26 g.) was added to *iso*propanol (250 ml.) in which aluminium (4·5 g.) had been dissolved, and the mixture slowly distilled through the Fenske column until the distillate was free from acetone (7 hours). Treatment of the residue with warm dilute sulphuric acid (1 l. of N.) until decomposition of the aluminium complex was complete afforded an oil which solidified and was collected by filtration. By crystallisation from light petroleum (b. p. 40—60°) at room temperature and at 0°, it was separated into a yellow, viscous oil (A) and solid 13-*hydroxy*-14-*methoxydocosanoic acid* (B) in the form of colourless prisms, m. p. 50—51° (Found: C, 71·4; H, 11·6. $C_{23}H_{46}O_4$ requires C, 71·5; H, 11·9%).

Brassidic and Erucic Acids.—(*a*) The foregoing oily reduction product (A; 6 g.) was dissolved in toluene (100 ml.), and the solution saturated with dry hydrogen bromide and left overnight. The mixture was then heated to 80° and kept at this temperature with passage of hydrogen bromide for 6 hours. The oil, obtained after removal of solvent, was dissolved in ethanol (25 ml.), and the solution added to zinc dust (10 g.). The mixture was boiled under reflux with periodic addition of alcoholic hydrogen chloride (5 ml. of 4N. in all) for 3 hours. Decantation of the solution from zinc and dilution with water furnished an oil which was isolated with benzene. The combined organic extracts were washed with aqueous sodium hydrogen carbonate and distilled to give, after a small fore-run, an unsaturated ester, b. p. 178—182°/0·3 mm., n_D^{20} 1·4530 (3 g.). Hydrolysis of the latter with aqueous alcoholic sodium hydroxide afforded a crude acid, m. p. *ca.* 50°, which was dissolved in boiling ethanol (9 ml.). Cooling of this solution to 20° gave crop (A) (1·2 g.), to 0° crop (B) (0·2 g.), and to −50° crop (C) (0·15 g.). Crop (A) had m. p. 60° and was substantially pure brassidic acid; it separated from ethanol in colourless, lustrous plates, m. p. 60·5°, undepressed by admixture with authentic material (Found: C, 77·8; H, 12·4. Calc. for $C_{22}H_{42}O_2$: C, 78·1; H, 12·4%). It furnished a *p*-bromophenacyl ester which crystallised from ethanol in plates, m. p. 74,° undepressed by admixture with authentic material, and gave, on treatment with peracetic acid (Dorée and Pepper, *loc. cit.*), the corresponding dihydroxybehenic acid, m. p. and mixed m. p. 131°. Crop (B) was a mixture of (A) and (C) and was not investigated further. Crop (C) (m. p. 28—30°) was dissolved in ethanol (5 ml.), and excess of aqueous lithium hydroxide added at the b. p. On cooling, the beautifully crystalline lithium salt of erucic acid (150 mg.) separated. Decomposition with acid in the presence of light petroleum (b. p. 40—60°) furnished almost pure erucic acid (85 mg.) (Found: equiv., 337. Calc. for $C_{22}H_{42}O_2$: equiv., 338), m. p. 31°, raised to 31—32° by admixture with a specimen of the natural material. It formed a *p*-bromophenacyl ester, m. p. 62°, and a dihydroxybehenic acid, m. p. 98°, both undepressed by admixture with samples prepared from the natural material.

(*b*) A stream of hydrogen bromide was passed through the molten 13-hydroxy-14-methoxydocosanoic acid (B) (1·2 g.) at 150—160° for 6 hours. The residue was treated with ethanol and zinc as before and, in view of the small quantity available, was hydrolysed directly with alkali to give crude brassidic acid (0·4 g.), m. p. 58—59°. Crystallisation from ethanol furnished pure brassidic acid in plates, m. p. 60°, undepressed by authentic material.

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40. *Electrolytic Dissociation Processes. Part VI. The Dielectric Polarisation of Iodine Cyanide and the Ionisation of the Cyanogen Halides.*

By FRED FAIRBROTHER.

Iodine cyanide undergoes a polarisation in an electron-donor solvent, similar to that shown by molecular iodine. Measurements have been made of its dielectric polarisation in carbon tetrachloride, benzene, dissobutylene, and dioxan, and of the ultra-violet light absorption in carbon tetrachloride, dissobutylene, and dioxan. The behaviour of the cyanohalogens as halides or as cyanides is due, not to differences in type of bonding, but to differences in solvent–solute interaction in a basic solvent and to the energy relationships involved in ionisation and in the particular reactions.

THE observation that the homopolar valency bond in molecular iodine becomes polarised on dissolution of the iodine in a medium which possesses some basic or electron-donor character,

even though of low dielectric constant, such as dioxan, benzene, *p*-xylene, or an olefin (Fairbrother, this series, Part V, *J.*, 1948, 1051) suggested that a similar phenomenon might be observed with iodine cyanide, especially if the structure implied by this name, *i.e.*, I^+CN^- made a substantial contribution to the structure of the molecule. The chemical reactions of an aqueous solution of this compound give support to this possibility. Even the usual method of preparation from molecular iodine and an alkali cyanide, viz., $I_2 + CN^- \rightleftharpoons ICN + I^-$, a reaction which is reversed in acid solution, suggests that it is formed in the first place by the union of a cyanide ion with a positive univalent iodine cation stabilised in alkaline solution by the electron-donor hydroxyl ions.

The dielectric polarisation of ICN has now been measured in carbon tetrachloride, benzene, di*iso*butylene, and dioxan, in which, if we assume an electronic polarisation of 19·0 c.c. and neglect the unknown atomic polarisation, the dipole moments are respectively 3·64, 3·76, 4·01, and 4·40 D. In none of these solvents did ICN exhibit appreciable conductivity.

The experimental data are recorded in the following tables, in which w_2 is the weight fraction of solute, f_2 the mol.-fraction of solute, ε the dielectric constant, d_4^{25} the density, and P_2 the molar solute polarisation.

ICN in carbon tetrachloride.

$w_2 \times 10^4$.	f_2.	ε.	d_4^{25}.	P_2 (c.c.).
0	0·000	2·2268	1·5847	—
1469	0·001477	2·2510	1·5851	288
1549	0·001558	2·2526	1·5854	289
2071	0·002090	2·2619	1·5856	292
2698	0·002713	2·2727	1·5860	292
3226	0·003235	2·2826	1·5863	297
			Average	292

$P_2 = 273 \pm 2$ c.c.; $\mu = 3{\cdot}64$ D.

ICN in benzene.

$w_2 \times 10^4$.	f_2.	ε.	d_4^{25}.	P_2 (c.c.).
0	0·000	2·2727	0·8732	—
8,222	0·004216	2·3577	0·8780	308
12,852	0·006605	2·4082	0·8804	311
14,056	0·007228	2·4219	0·8813	311
24,462	0·01264	2·5423	0·8874	312
24,584	0·01271	2·5454	0·8877	313
			Average	311

$P_2 = 292 \pm 1$ c.c.; $\mu = 3{\cdot}76$ D.

ICN in di*iso*butylene.

0	0·000	2·0891	0·7134	—
3589	0·002635	2·1206	0·7151	353
3723	0·002733	2·1218	0·7153	350
4393	0·003227	2·1276	0·7156	351
5334	0·003919	2·1364	0·7162	352
			Average	351·5

$P_2 = 332{\cdot}5 \pm 1$ c.c.; $\mu = 4{\cdot}01$ D.

ICN in dioxan.

0	0·000	2·2124	1·0275	—
11,934	0·006910	2·4062	1·0351	404
13,275	0·007690	2·4250	1·0358	398
16,355	0·009487	2·4784	1·0378	398
20,558	0·01195	2·5458	1·0404	391
21,572	0·01254	2·5639	1·0411	391
28,664	0·01671	2·6970	1·0457	379
30,563	0·01780	2·7097	1·0469	377

$_\infty P_2 = 420$ c.c.; $_\infty P_2 = 401$ c.c.; $\mu = 4{\cdot}40$ D.

The polarisations and moments have been calculated by the usual Clausius–Mosotti–Debye method. Only in dioxan was there any noticeable change of polarisation with concentration, and in this the molar solute polarisations were extrapolated to infinite dilution against the weight fraction w_2; in the remaining solvents the polarisations were averaged. The extrapolation to infinite dilution of the dielectric constants and densities of the solutions, with a view to using the respective intercepts as solvent parameters (cf. Halverstadt and Kumler, *J. Amer. Chem. Soc.*, 1942, **64**, 2988), gave results which were not significantly different from measurements on the pure solvents, which were therefore used in the calculations. A single large sample (2—3 l.) of each solvent was used for all measurements and kept throughout with its vapour in contact with anhydrous magnesium perchlorate (Fairbrother, *J.*, 1945, 503). Cryoscopic measurements in benzene by Zappi (*Bull. Soc. chim.*, 1930, **47**, 453) and distribution measurements between water and carbon tetrachloride by Yost and Stone (*J. Amer. Chem. Soc.* 1933, **55**, 1889) indicate a normal molecular weight for ICN in these solvents; we may presume the like for the remaining two.

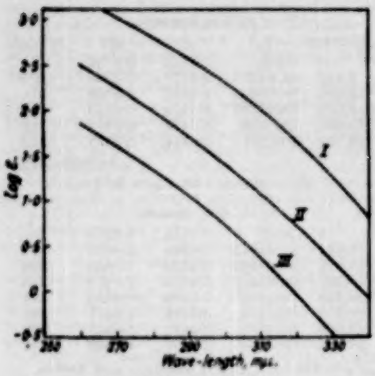
There do not appear to be any recorded measurements of the dielectric polarisations of ICN in the vapour state. Zwartsenberg and Ketelaar (*Rec. Trav. chim.*, 1942, **61**, 877) have measured the dipole moment in benzene solution, which solvent they state "was chosen because solutions in other solvents showed a considerable electrical conductivity." They obtained a value of $\mu = 3{\cdot}82$ D. by the usual Debye method, neglecting atomic polarisation, or $\mu = 3{\cdot}77$ D. assuming an atomic polarisation of 8·3 c.c., which was derived as the mean of the atomic polarisation in molecular iodine and in molecular cyanogen. This method of averaging P_2 however, implies an additive character which is not strictly justifiable, and in the absence of direct evidence, the atomic polarisation of ICN must be regarded as an unknown quantity.

For comparison, therefore, the dipole moments in the several solvents have been calculated

with the neglect of atomic polarisation, inclusion of which may reduce the moments given by something under 0·05 Debye unit. The electronic polarisation (Na_D) has been taken as 19·0 c.c. On the one hand, the sum of the partial refractivities of covalently bonded iodine (Eisenlohr, *Z. physikal. Chem.*, 1911, **75**, 585) and of CN derived from the molar refractivity of HCN (Watson and Ramaswamy, *Proc. Roy. Soc.*, 1936, *A*, **156**, 144) is (13·90 + 5·16) = 19·06 c.c., whilst direct determinations of the refractivity, for Na_D, give 19·00 ± 0·05 c.c. in benzene (Zwartsenberg and Ketelaar, *loc. cit.*) and a mean of 19·10 c.c. in alcohol and chloroform (Zappi, *Bull. Soc. chim.*, 1930, **47**, 537).

It may be observed that dissolution of ICN in the electron-donor solvents causes a significant increase in dielectric polarisation; in dioxan it is over 40% greater than in carbon tetrachloride. ICN is very freely soluble in dioxan but only about 0·5 g. dissolves in 100 g. of carbon tetrachloride. It may also be observed that, as with molecular iodine, the π electrons of the ethylenic bond in *di*isobutylene are more effective in bringing about the polarisation than the aromatic electrons of benzene.

Further evidence of solvent–solute interaction is provided by the ultra-violet light absorption of ICN in these solvents. In the case of molecular iodine the shift in the absorption on dissolution in a donor solvent is apparent to the unaided eye; iodine cyanide absorbs only in the ultra-violet.



I. *Carbon tetrachloride.*
II. *Diisobutylene.*
III. *1 : 4-Dioxan.*

The ultra-violet light absorption of ICN and BrCN in ethanol and chloroform was studied by Gillam (*Trans. Faraday Soc.*, 1933, **29**, 1132), who found that the absorption curve of ICN, which discloses no maximum down to 240 mμ, is displaced towards the shorter wave-lengths in ethanol as compared with chloroform. There was no evidence of a similar shift in BrCN.

The ultra-violet light absorption of solutions of ICN in carbon tetrachloride, diisobutylene, and dioxan has now been measured by a Beckman photoelectric spectrophotometer. The absorption curves (see figure) show a marked displacement towards the shorter wave-lengths in the electron-donor solvents.

Since the bond moment of $^-$CN in the alkyl cyanides is >3 D., the carbon being positive to the nitrogen, whilst the bond moment of $^-$I in the alkyl iodides is ~1·5 D., the carbon being positive to the iodine, the magnitude of the moment of ICN suggests that in this molecule the iodine atom is the positive end of the dipole. In ICN, therefore, unless the $^-$CN moment is greatly increased, the iodine is much more positive (or less negative) towards the carbon than in the alkyl iodides and co-ordination with donor solvent molecules would be expected to increase the dielectric polarisation, which in fact does occur.

This is further supported by a consideration of the interatomic distances in ICN. These have recently been measured very accurately by Smith, Ring, Smith, and Gordy (*Physical Rev.*, 1948, **74**, 370) by a micro-wave technique. They find the C–I internuclear separation to be 1·995 A., which is considerably shorter than the separation in methyl iodide, 2·139 A. (Gordy, Simmons, and Smith, *ibid.*, p. 243). This they attribute "largely to resonance between the electronic structures $\overset{+}{\text{X}}\!=\!\text{C}\!=\!\text{N}$ and $\text{X}\!-\!\text{C}\!\equiv\!\overset{-}{\text{N}}$ which gives the X–C bond some double character."

It is probable that in all the so-called cyanogen halides, the halogen atom is the positive end of the dipole of the gaseous molecule, with a decrease in moment ICN > BrCN > ClCN. There is experimental evidence of the smaller dipole moment of the bromide in benzene solution, 3·13 D. as compared with 3·82 D. (Zwartsenberg, *Rec. Trav. chim.*, 1943, **62**, 148).

The nature of the valency bonds in iodine cyanide and other cyanohalogens has given rise to much discussion (cf. Gmelin, "Handb. anorg. Chem.," 8th Edn., Berlin, 1933, No. 8, p. 457), chiefly based upon their chemical reactions, which have been studied by a number of workers and have led to conflicting theories.

Iodine cyanide is essentially an oxidising agent in aqueous solution, being unaffected by other oxidising agents and giving, when reduced, either free iodine or iodide ion

according to the strength and excess of the reducing agent, *e.g.*, $2ICN + H_2SO_3 + H_2O = 2HCN + H_2SO_4 + 2HI$ (Chattaway and Wadmore, *J.*, 1902, **81**, 191) and $ICN + AsO_3^{3-} + 2OH^- = CN^- + AsO_4^{3-} + I^- + H_2O$ (Gutman, *Z. anal. Chem.*, 1924, **65**, 246), iodine being liberated in each case if the ICN is in excess.

If a solution of ICN in carbon tetrachloride or benzene is shaken with an aqueous solution of ferrous sulphate, the organic solvent slowly takes on the characteristic colour of free iodine. An aqueous solution is apparently unaffected by dilute sulphuric acid, but if it is made slightly alkaline and allowed to stand a few moments, on acidification free iodine is separated. Similarly, if pyridine is added to an aqueous solution, a yellow colour quickly develops and again iodine is precipitated on acidification. These latter reactions are presumably due to the formation of iodide and iodate from the unstable IOH or PyIOH respectively, and the subsequent oxidation of the iodide ion by the iodate on acidification. It is to such formation of iodide that the few reactions reported in which ICN behaves as an iodide are doubtless due. Thus, Normand and Cumming (*J.*, 1912, **101**, 1852) report that an aqueous solution of silver acetate very slowly gave a precipitate which was a mixture of silver cyanide, iodide, and iodate and that, when potassium hydroxide was added to the original solution, a copious precipitate of silver iodide appeared.

The reactions of ICN are essentially those of a cyanide of positive iodine: ClCN in contrast behaves as a chloride of cyanogen.

Zappi (*loc. cit.*, p. 453) has pointed out a number of differences between the reactions of ICN and ClCN: that silver nitrate does not react, or reacts very feebly, with ICN dissolved in water, alcohol, ether, or chloroform, but that ClCN slowly reacts, all the chlorine being ultimately precipitated after the lapse of 2—3 hours; that ICN is completely dissociated in (halogen)-acid solution, $ICN + HI = I_2 + HCN$, and (on gentle warming) $ICN + HCl = HCN + ICl$; that ICN gives iodate with potassium hydroxide (as observed by Nef, *Annalen*, 1895, **287**, 316) and a quantitative yield of iodine with potassium iodide, the cyanogen in both cases appearing as potassium cyanide, but that ClCN does not give chlorate or cyanide with potassium hydroxide, or chlorine with HCl; that whilst a ferrous–ferric mixture gives an abundant cyanide reaction with ICN, it gives a completely negative result with ClCN. (It may be noted that the Prussian-blue test is not given on addition of a solution of ICN to one containing ferrous and ferric salts unless it is first made alkaline and subsequently acidified.) Zappi concluded that such facts seem to indicate a difference in constitution between the two compounds.

Striking as these differences in reaction are, they do not, however, form conclusive evidence that there is any fundamental difference *in kind* between the valency bonds in ClCN and in ICN. Indeed, the physical evidence indicates otherwise. Badger and Woo (*J. Amer. Chem. Soc.*, 1931, **53**, 2573) found that the ultra-violet absorption was of the same type for ClCN, BrCN, and ICN, and West and Farnsworth (*J. Chem. Physics*, 1933, **1**, 402) showed that the Raman spectrum of all three compounds is similar.

The manner in which a given molecule will ionise is not a unique function of the structure of the molecule itself, but also of its environment; this behaviour is familiar as amphoteric reaction in acid–base systems.

Consider the alternative modes of ionisation of ClCN and ICN in a pure solvent. The energies involved in the ionisation and subsequent electrolytic dissociation may be divided into the following steps:

(A) Formation of halide anions and cyanogen cations:

$$e.g.,\ ICN \xrightarrow{a} I_g + CN_g \xrightarrow{b} I_g^- + CN_g^+ \xrightarrow{c} I_s^- + CN_s^+$$

(*a*) Energy of dissociation of dissolved ICN to $I_g + CN_g$.
(*b*) Ionisation potential of $CN_g \longrightarrow CN_g^+$ − electron affinity of $I_g \longrightarrow I_g^-$.
(*c*) Sum of solvation energies of CN_g^+ and I_g^-.

(B) Formation of halide cations and cyanogen anions:

$$e.g.,\ ICN \xrightarrow{a'} I_g + CN_g \xrightarrow{b'} I_g^+ + CN_g^- \xrightarrow{c'} I_s^+ + CN_s^-$$

(*a'*) Energy of dissociation of dissolved ICN to $I_g + CN_g$.
(*b'*) Ionisation potential of $I_g \longrightarrow I_g^+$ − electron affinity of $CN_g \longrightarrow CN_g^-$.
(*c'*) Sum of solvation energies of I_g^+ and CN_g^-.

Since a and a' are the same, the course of the ionisation is determined by whether $(c - b)$ or $(c' - b')$ is the greater. In NaCN and KCN, which have a rock-salt structure at room temperature, the CN^- ion is believed to achieve spherical symmetry by rotation. The edge of the unit cell in KCN is closely similar to that in KBr, so that the rotating CN^- ion must have an effective radius which is close to that of the Br^- ion (cf. Verweel and Bijvoet, *Z. Krist.*, 1938, **100**, 201; and W. G. Palmer, "Valency," Cambridge, 1944, p. 54). It seems probable, therefore, that the ionisation potential and electron affinity of the cyanogen radical may also be similar to those of the bromine atom. The chlorine atom, however, is very much smaller than the iodine atom, its ionisation potential is 2·35 volts greater and its electron affinity 0·53 volt greater than those of iodine.

Consequently, whilst the ionisation of ClCN into Cl^+ and CN^- may be much more endothermic than into ^-Cl and CN^+, the ionisation of ICN into I^+ and CN^- may be less difficult than into I^- and CN^+. The differences in heats of solvation of the ions in the respective alternatives would be insufficient to overcome the difference in endothermicity in the case of ClCN. It follows, therefore, that there should be few if any reactions in which ClCN behaves as a cyanide, but a number in which the energies of solvation or reaction of the resulting ions will be sufficient to bring about the ionisation and reaction of ICN as a cyanide.

In computing the energies of solvation of the cations, it is necessary to take into account not only the electrostatic energy of solvation in a chemically indifferent medium, but also the possibility of bond formation between solvent and solute molecules. This will be especially significant in basic, or electron-donor solvents, which are able to form a co-ordinate bond with a halogen cation.

It would appear that water in itself is not sufficiently basic to bring about the appreciable ionisation of ICN, as shown by the lack of reaction with silver nitrate. This, however, may occur in a much more basic solvent or in aqueous solution in the presence of a strongly electron-donor solute species such as hydroxyl ion.

Clark and Streight (*Trans. Roy. Soc. Canada*, 1928, **22**, [3], 323) report that electrolysis of 0·1M-solutions of ICN in a number of carefully dried organic solvents, acetamide, benzene, acetonitrile, nitrobenzene, methanol, ethanol, nitromethane, aniline, and quinoline, gave iodine at the *anode* and cyanide or cyanogen or paracyanogen at the cathode, but that solutions in pyridine gave iodine at the *cathode* and cyanide at the anode, and that on addition of water iodine again appeared at the anode. It is probable, however, that the last observation was due to the secondary decomposition into iodide and iodate as described above.

The electrical conductivity of iodine cyanide in pyridine was studied carefully by Audrieth and Birr (*J. Amer. Chem. Soc.*, 1933, **55**, 668), who found that it increases with time to give maximum values. The experimental evidence indicated that the reaction between solvent and solute resulted in the primary formation of a non-conducting addition compound which in time changes over into a true quaternary pyridinium salt, 1-iodopyridinium cyanide. A similar mechanism the formation of 1-iodopyridinium iodide would account for the conductivity of molecular iodine in pyridine.

This reaction of pyridine and its stabilising effect on the positive iodine is paralleled by its behaviour in stabilising the univalent iodine cation in the salts prepared by Carlsohn (*Angew. Chem.*, 1932, **45**, 580; 1933, **46**, 747) and by the abnormal positive heat of solution of iodine in pyridine. Heats of solution of iodine in a variety of solvents have recently been measured accurately by Hartley and Skinner (to be published); they find that whereas in hydrocarbons and a number of oxygen-containing solvents, the heat of solution of iodine is negative, yet in pyridine it is positive. A simple test-tube experiment shows that the heat of dissolution of ICN in pyridine is also positive.

BrCN, which occupies an intermediate position, is stated to be un-ionised in water, neutral to litmus, and to give no precipitate with silver nitrate solution. It is soluble in cold concentrated sulphuric, hydrochloric, or nitric acid without decomposition, but is instantly hydrolysed by aqueous alkali hydroxides or carbonates into cyanide, bromide, and bromate; bicarbonates have no action (Williams, "Cyanogen Compounds," London, 1948, 9). Its ultra-violet light absorption (Gillam, *loc. cit.*) shows that there is much less solvent–solute interaction in ethanol than in the case of ICN. Clark and Streight (*loc. cit.*), using Sampey's method (*J. Amer. Chem. Soc.*, 1927, **49**, 2849) for the quantitative determination of positive halogen by titration with stannous chloride, report that BrCN repeatedly titrated as if it contained 89·2% of positive bromine, whilst iodocyanogen gave results corresponding to 99% of positive iodine.

It is to be concluded, therefore, that the positive iodine cation does not pre-exist in the free

ICN molecule, but is formed as it is in molecular iodine, either by a solvolytic ionisation alone in a very basic solvent like pyridine, or in other solvents by the action of some strongly electron-donor species in solution such as the hydroxyl ion in its alkaline hydrolysis, and that the contrasting behaviour of ClCN is not due to any great difference in the electronic structures of the free molecules, but to differences of solvent–solute interaction and of the energies involved in the particular reactions.

Experimental.

Materials.—Iodine cyanide was prepared in the usual manner by the slow addition of iodine to concentrated aqueous potassium cyanide, followed by cooling in a refrigerator, filtration, washing and drying of the crystals. The crude product was purified by sublimation in a current of dry nitrogen, and samples were freshly re-sublimed at a comparatively low temperature immediately before each determination. The final product was snow-white.

Solvents.—Benzene (b. p. 80·1° ± 0·1°/762 mm.), dioxan (b. p. 100·2—100·6°/774 mm.), and diisobutylene (b. p. 101·0—102·5°/757 mm.) were purified as described in Part V (*J.*, 1948, 1051). (The diisobutylene boiled over a wider range and differed in both dielectric constant and density from that used in Part V, which was from a different source.) Carbon tetrachloride, "for medicinal purposes" (Allbright and Wilson), was dried by long contact with phosphoric oxide and fractionated through an efficient column in a stream of dry nitrogen; b. p. 76·4° ± 0·2°/762 mm.

Measurements.—Dielectric constants and densities were measured at 25·00° as previously described (Part IV, *J.*, 1945, 503).

I am indebted to Messrs. Imperial Chemical Industries Ltd. for a grant for the purchase of apparatus.

The University of Manchester. [*Received, August 19th*, 1949.]

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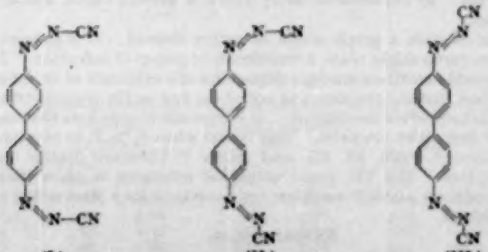
41. *The Isomerisation of Labile Diphenyl-4 : 4'-bisdiazocyanide in Solution.*

By D. D. Brown, R. J. W. Le Fèvre, and R. N. Whittem.

The two *known* isomers of the molecule named in the title are "*cis-cis-*" and "*trans-trans-*"; a third variety, "*cis-trans-*," should exist but is so far unknown. If the spontaneous formation of the stable from the unstable forms involved simultaneous configurational inversions, the situation would be explicable. However, the process is now found to proceed by a more complex mechanism. Whilst, in benzene solution, it appears to follow first-order kinetics with an activation energy of 26·9 kcals./g.-mol., in the polar solvents *o*-dichlorobenzene, pyridine, and nitrobenzene the reaction is not of the first order. The suggestion is therefore made that the reaction consists of two consecutive first-order inversions, with the "*cis-trans-*" compound as an intermediate. This requires the assumption that, in benzene solution, the rate of one of these inversions is not significant kinetically and that the overall change in this solvent is governed by only one of the two rates.

On Hantzsch's theories of the configuration of the $-N{=}N-$ group, diphenyl-4:4'-bisdiazocyanide should exist in three isomeric forms, (I), (II), and (III):



(I.) (II.) (III.)

In fact, only two are known (Euler, *Chem. Zentr.*, 1907, i, 1572; Le Fèvre and Vine, *J.*, 1938, 1878; Anderson, Le Fèvre, and Savage, *J.*, 1947, 445). Chemical and physical evidence (Le Fèvre *et al.*) favours the view that the variety with m. p. 97—98° is *cis-cis-* (I) whilst that with m. p. 208—209° is *trans-trans-* (III).

The *cis-trans-*species (II) remains, so far, unknown, notwithstanding the experimental fact

that the spontaneous change of (I) into (III) proceeds quite slowly in the dissolved state (Le Fèvre and Vine, *loc. cit.*). In addition to the work already recorded by Le Fèvre and Northcott (this vol., p. 944) attention has therefore been directed to the kinetics of the production of (III) from (I) in a hope that indications concerning (II) might thereby be revealed.

At the outset there appeared three possibilities. These were: (*a*) that (I) passes directly into (III) by two simultaneous first-order reactions of equal velocities; (*b*) as (*a*) except that the velocities are unequal; and (*c*) that two consecutive first-order reactions ($I \xrightarrow{k_1} II \xrightarrow{k_2} III$) are involved.

Case (*a*), if relevant, would explain the absence of isomer (II); it requires that (I) $\longrightarrow$ (III) should appear to be of first order. One would predict that the activation energy needed in such a process is in the region of 46 kcals./g.-mol., *i.e.*, twice that required by each separate azo-inversion.

Case (*b*) seemed a reasonable contingency. As soon as the isomerisation commences, the environmental (polarisation and polarisability) factors for the second $-N{=}N-$ cannot be exactly as before. Each azo-group will be under a varying influence, from the other end of the molecule, during the actual act of inversion. Separate molecules, however, would behave similarly and the overall rate (as observed) should still be of the "first order."

Case (*c*) seemed the most likely mechanism. This would require the reacting molecules to possess, at any one time, only that activation energy necessary for one azo-inversion. If the quantity $e^{-E/RT}$ represents the probability of a molecule having energy in excess of E then the probability of a molecule having energy in excess of $2E$ will be roughly only $1/e^{E/RT}$ of the first probability. The chance then, that a molecule will react by a consecutive mechanism would appear to be far greater than the chance of both azo-groups being inverted simultaneously.

To follow a consecutive reaction, involving three molecular species, by the variation of an additive physical property the concentrations of (I), (II), and (III) may be written in terms of A_1, the initial concentration of (I) and the two constants k_1 and k_2:

$$(C_I)_t = A_1 e^{-k_1 t}$$
$$(C_{II})_t = A_1 k_1 (e^{-k_1 t} - e^{-k_2 t})/(k_2 - k_1)$$
$$(C_{III})_t = A_1 [1 - (k_2 e^{-k_1 t} - k_1 e^{-k_2 t})/(k_2 - k_1)]$$

The second equation has a maximum value dependent on the ratio $r = k_2/k_1$:

$$(C_{II})\text{max.} = [A_1 r/(1 - r)][e^{-r \ln r/(r-1)} - e^{-\ln r/(r-1)}]$$

If the rate displaying property, X, is one which, for each solute separately in dilute solution, conforms to the equation: $X_{SI} = X_S(1 + aw_1)$, where X_S refers to the solvent, X_{SI} refers to the solution of (I), and w_1 is the weight fraction of solute (I), and if the property is additive for a solution containing a mixture of the three solutes, such that:

$$X_{SI,II,III} = X_S(1 + aw_1 + \beta w_2 + \delta w_3)$$

then it is obvious that, in the present problem, a graph of $X_{SI,II,III}$ against time will be, in effect, the sum of three curves: an exponential decay curve, a growth curve, and a curve with an intermediate maximum.

The interpretation of such a graph would be rather limited. If X_{SII} were much greater than X_{SI} and X_{SIII} the curve might show a maximum or points of inflection. The presence of such characteristics would constitute strong evidence for the existence of an intermediate form. In their absence, the fact that the reaction was not of the first or the second order would remain the only evidence for a consecutive mechanism. It is relevant to note here that some consecutive reactions *appear* to be first-order reactions. This occurs when $k_1 \gg k_2$ or *vice versa*, but Walker (*Proc. Roy. Soc. Edinburgh*, 1898, **22**, 23), and Mellor ("Chemical Statics and Dynamics," Longmans, 1904, Chapters V and VI) quote numerical examples to show that r needs to be greater than 100 to produce a passable semblance of constancy for k (first order) over all but the early stages of the reaction.

Experimental.

The 4 : 4'-diphenylbisdiazocyanides were found to be best prepared by the following slight modification of the directions of Anderson, Le Fèvre, and Savage (*loc. cit.*). The benzidine was first purified by several recrystallisations from alcohol, then converted (5 g. in 40 c.c. of EtOH) into the dihydrochloride by adding 10N-HCl (18 c.c.) to its hot solution, and bisdiazotised ($NaNO_2$, 3·9 g.; H_2O, 60 c.c.) at 5—10°. The clear resultant liquid was well stirred with chloroform, the whole cooled below −10° (carbon dioxide–alcohol), daylight excluded, and sodium cyanide (3 g. in the minimum amount of water) added. The heavy layer was then quickly separated, washed with water, and run into twice its volume of light petroleum at −30°.

The product, after rapid filtration, was dried, and stored *in vacuo* in the dark. The stable isomeride could be obtained by concentrating the filtrates after they had been kept for several days at room temperature.

Velocity measurements by the dielectric method were made difficult by the relative insolubility of the stable form causing, in most solvents, crystallisation to occur before the reaction had progressed a useful distance. To prevent this, initial concentrations were reduced, but the capacity changes were then so small that their accurate determination required apparatus with a high degree of frequency stability and temperature control. The dielectric-constant method was eventually abandoned in favour of a photometric method. For this latter method the Hilger Spekker-absorptiometer was used, the rate-displaying property being the change in the quantity of light absorbed by the solution from a narrow band of pre-selected wave-lengths. To enable a suitable light range to be chosen for each medium, spectral transmissivities of the two separate forms as solutes were first explored (see later), and of the filters supplied by the makers, those passing the band 5600—6100 A. used with benzene and those passing 4800—6200 A. for the other solvents.

In benzene, the maximum concentration that could be used was 0·06%. Crystallisation of the *trans-trans*-compound occurred at higher concentrations. The necessity for using such dilutions limited the accuracy of the measurements. Readings were taken by pouring 30 c.c. at a time from the main reaction flask (painted black to exclude all light) into a 4-cm. cell. The null point was observed at once, under a standard procedure, and with the shutter reset for the pure solvent before each reading. The logarithmic scale of the instrument was first calibrated for known mixtures of *cis-cis-* and *trans-trans*-forms. For benzene solutions, a linear relation was obtained between the scale reading and the concentration of *cis-cis-* in the presence of *trans-trans*-forms. Slight departures from linearity were found to exist in the calibration curves for the other solvents. Now, if at all times during the isomerisation only two molecular species were present, as would be the case in processes (*a*) and (*b*), the rate-displaying property chosen above could be used in determining the kinetics of the reaction. This would also apply to process (*c*) if $r > 100$. In the presence of a third molecular species there would be no way of relating scale reading to concentration and any attempt to obtain constant k values from either first- or second-order equations should fail. Such failure to obtain constant k values would be, in itself, evidence for a consecutive mechanism.

Results.

Roughly, "half-change" times seem to be independent of the initial concentration (cf. Table I). However, despite this, in nitrobenzene (as also in pyridine or *o*-dichlorobenzene) the reaction is unlikely to be truly of the first order, since k, if appropriately evaluated for each observational time interval, is not constant (Table II): On the other hand, in benzene, the values of k, if similarly calculated, do appear almost invariant, and lead to an apparent activation energy for the change of 26·9 kcals./g.-mol. These statements are illustrated in the figure. From these facts we draw the conclusions set out in the last two sentences of the "Summary" to this paper.

Table I.

Solvent.	Initial concn.	Temp.	Time for ½ change.
$C_6H_5{\cdot}NO_2$	5·4 g./litre	25°	9·5 hr.
,,	6·1 ,,	,,	8·9 ,,
,,	7·8 ,,	,,	9·0 ,,
C_6H_4 ,,	0·03 wt.-%	35	3·9 ,,
,,	0·03 ,,	,,	3·7 ,,
,,	0·05 ,,	,,	4·0 ,,
,,	0·03 ,,	25	18 ,,
,,	0·05 ,,	25	16 ,,

Table II.

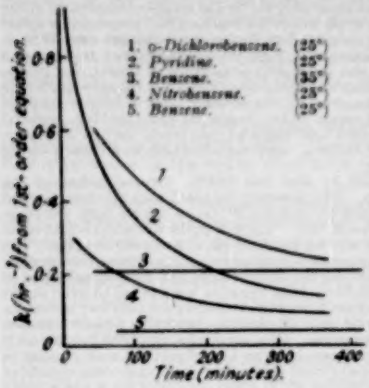
Variation of k *with time.*

(k calculated from first order equation; $kt = \ln[a/(a - s)]$).

$C_6H_5{\cdot}NO_2$. 25°.		Pyridine. 25°.		*o*-Dichlorbenzene. 25°.		Benzene. 35°.		Benzene. 25°.	
Time, min.	k.	Time, min.	k.	Time, min.	k.	Time, min.	k.	Time, min.	k.
16	0·300	9	0·94	22	0·49	73	0·22	122	0·041
56	0·224	44	0·55	44	0·60	200	0·19	255	0·051
74	0·208	64	0·46	75	0·53	307	0·22	301	0·048
93	0·180	87	0·39	122	0·43	370	0·21	414	0·048
143	0·151	116	0·33	209	0·33			1267	0·060
171	0·137	189	0·23	309	0·26			2960	0·039
1289	0·057	1340	0·06	1361	0·16				

Visual Absorption Spectra of the Labile and Stable Forms.—For reasons explained by Le Fèvre and Wilson (this vol., p. 1106) when reporting the ultra-violet absorption spectra of isomeric pairs of benzenediazocyanides, we took the opportunity, during the process of filter selection

(see above), to make qualitative comparisons of the absorbing properties of the two bisdiazocyanides of the present work towards visible light. Equivalent solutions (sometimes prepared directly and sometimes by allowing complete thermal change to occur in the dark) of various concentrations in *cyclo*hexanone or nitrobenzene were examined in the Hardy recording spectrophotometer. The wave-length range accessible covered only 4000—7000 A., and since in no cases have the automatic traces traversed an absorption peak they are not reproduced. For each pair of solutions, however, the following facts were consistently and definitely displayed: (*a*) the point at which 100% absorption ceased was further towards the red end of the spectrum for the stable form; and (*b*) the general slope of the %-transmittance–wave-length curves was slightly steeper for the unstable form. We are satisfied, therefore, that the type and degree of spectral differences (*i.e.*, of intensity and $\lambda_{max.}$), mentioned by Le Fèvre and Wilson (cf. also Le Fèvre, Northcott, and Wilson, *Chem. and Ind.*, 1948, 732), occur also for the present cases. It is relevant to recall that in the solid state the stable variety is maroon-coloured, in contrast to its isomer, which is orange (Anderson, Le Fèvre, and Savage, *J.*, 1947, 451).



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42. *Some Amidines and Dihydroglyoxalines of the* 1 : 1-*Diphenylethane and* 1 : 1-*Diphenylpropane Series.*

By J. O. JÍLEK and M. PROTIVA.

In view of the well-known similarity of the pharmacological properties between ethyldialkylamines and 2-methyldihydroglyoxaline derivatives 2-(2 : 2-*diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI) has been prepared as a glyoxaline analogue of "Aspasan" (V). Three similar amidines (VIII) and two lower homologues (IX and X) have also been prepared, one of them (VIII; R = H) exerting a relatively strong antihistaminic action.

DJERASSI and SCHOLZ (*J. Amer. Chem. Soc.*, 1947, **69**, 1688) noticed the analogy between the known antihistaminic agents "Antergan" (I) and "Antistin" (II). (II) differs from (I) only in that the 2-methyldihydroglyoxaline group replaces the dimethylaminoethyl moiety.

$CH_2Ph{\cdot}NPh{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$ (I.)

$CH_2Ph{\cdot}NPh{\cdot}CH_2{\cdot}C{<}\begin{matrix}N{-}CH_2\\NH{-}CH_2\end{matrix}$ (II.)

Making use of this analogy, these authors prepared a series of aryloxyacetamidines and 2-aryloxymethyldihydroglyoxalines and found them to show antihistaminic activity similar to that of the corresponding aryloxyethyldialkylamines. On the basis of the same assumptions the dihydroglyoxaline analogue (IV) of "Benadryl" (III) was recently prepared almost simultaneously in different laboratories (Protiva and Urban, *Coll. Trav. chim. Tchécosl.*, 1948, **13**, 340; Cavallini and Mazzucchi, *Farmaco*, 1947, **2**, 273; Dahlbom and Sjögren, *Acta Chem. Scand.*, 1947, **1**, 777; Djerassi and Scholz, *J. Org. Chem.*, 1948, **13**, 830) and was found to be quite similar to (III) in its pharmacological properties.

$CHPh_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$ (III.)

$CHPh_2{\cdot}O{\cdot}CH_2{\cdot}C{<}\begin{matrix}N{-}CH_2\\NH{-}CH_2\end{matrix}$ (IV.)

Considering these results, it seemed desirable to prepare amidine and dihydroglyoxaline analogues of 3 : 3-diphenylpropylamine derivatives, another pharmacologically interesting

group characterised by "Aspasan" (V), showing antispasmodic and antihistaminic activity (Bockmühl and Ehrhart, *Annalen*, 1948, **561**, 52). Attention was paid first to the preparation

$CHPh_2{\cdot}CH_2{\cdot}CH_2{\cdot}N<[CH_2]_5$ (V.) $\quad CHPh_2{\cdot}CH_2{\cdot}C<\begin{matrix}N{-}CH_2\\NH{\cdot}CH_2\end{matrix}$ (VI.) $\quad Ph_2CH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$ (VII.)

of 2-(2 : 2-*diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI), the analogue of "Aspasan" (V). This compound was obtained from ββ-diphenylpropionitrile either through *ethyl ββ-diphenylpropionimidate hydrochloride* by the method of Klarer and Urech (*Helv. Chim. Acta*, 1944, **27**, 1762), or by fusion with 2-aminoethylammonium toluene-*p*-sulphonate (Oxley and Short, *J.*, 1947, 497). The first method yielded an impure hydrochloride, which by the action of ammonia gave the base (VI), m. p. 101°. From the base a crystalline *hydrochloride* (m. p. 88—90°) and *picrate* were prepared. By the second method, a crystalline *toluene-p-sulphonate* was obtained, which could be converted into the base and hydrochloride, identical with the products obtained by other route. The base, toluene-*p*-sulphonate, and picrate gave good analytical results; the hydrochloride in contrast, even when thoroughly dried *in vacuo*, gave results which indicated that it was a monohydrate. Since, however, it might have been ββ-diphenylpropiono-2-aminoethylamide hydrochloride (VII), which could be formed by opening the glyoxaline ring of (VI), the *base* (VII) was prepared from ethyl ββ-diphenylpropionate by the action of excess of ethylenediamine at 210—220° (Hill and Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 822). The hydrochloride of (VII) melts at 214—215° and differs from that having m. p. 88—90°. The base (VII) is a solid of m. p. 118°.

Three new ββ-diphenylpropionamidines (VIII; $NR_2 = NH_2$, NMe_2 and $N<[CH_2]_5$) of a similar type were prepared by the action of an excess of ammonia or of the appropriate amine on ethyl ββ-diphenylpropionimidate hydrochloride. For comparison *diphenylacetamidine* (IX) and 2-benzhydryl-4 : 5-dihydroglyoxaline (X) were also prepared by standard methods.

$CHPh_2{\cdot}CH_2{\cdot}C<\begin{matrix}NH\\NR_2\end{matrix}$ (VIII.) $\quad CHPh_2{\cdot}C<\begin{matrix}NH\\NH_2\end{matrix}$ (IX.) $\quad CHPh_2{\cdot}C<\begin{matrix}N{-}CH_2\\NH{\cdot}CH_2\end{matrix}$ (X.)

The soluble derivatives of compounds (VI), (VIII), (IX), and (X) were tested for antihistamine activity. Only the hydrochloride of (VIII; R = H) was found to be approximately equal in activity to "Aspasan" (0·1 unit of "Benadryl" activity). Further testing for antispasmodic, analgesic, and pressor activity is in progress.

Experimental.

M.p.s are corrected. Analytical samples were dried at 0·2 mm. (P_2O_5) for 10 hours at suitable temperatures. Semimicro-analyses were by Miss Bruchalová, Ing. Mňoucek, Dr. Kralíčková, and Ing. Rýpar.

ββ-Diphenylpropionitrile.—This was prepared from α-cyano-ββ-diphenylpropionic acid by the method of Kohler and Reimer (*Amer. Chem. J.*, 1905, **33**, 338) and purified by distillation *in vacuo* (Freeman, Ringk, and Spoerri, *J. Amer. Chem. Soc.*, 1947, **69**, 858) and by crystallisation from ethyl alcohol–light petroleum. Yield 72%. B. p. 175—178°/2 mm. M. p. 88·5°.

Ethyl ββ-Diphenylpropionimidate Hydrochloride.—A solution of the above nitrile (11·7 g.) in a mixture of chloroform (60 c.c.) and absolute ethyl alcohol (7·5 c.c.) was saturated with dry hydrogen chloride at 0° and set aside for 10 days in a closed flask at 20°. After removal of the solvents at 30° *in vacuo* a crystalline residue remained, representing the crude product of m. p. 128°, in quantitative yield.

2-(2 : 2-*Diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI).—(*a*) The above imidate hydrochloride (8·8 g.), absolute ethylenediamine (1·9 g.), and absolute ethyl alcohol (50 c.c.) were refluxed for 7 hours in a slow stream of dry air in a bath at 100—115°. After cooling, the solution was filtered from ethylenediamine dihydrochloride (0·1 g.; m. p. 335—338° (decomp.)) which separated. The filtrate was concentrated under reduced pressure, the oily residue dissolved in water (70 c.c.), and the solution filtered and treated with concentrated aqueous ammonia (7 c.c.). The *base* (4·4 g.) was filtered off and recrystallised from 50% ethyl alcohol. It had m. p. 84—86°, or, after drying (P_2O_5 *in vacuo*), m. p. 101° (Found: C, 81·2; H, 7·5. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·2%). In another similar experiment the crude oily hydrochloride was dissolved in acetone (10 c.c.) and the solution treated with absolute ether (10 c.c.). The oil which separated crystallised (7·5 g.). Crystallisation from acetone raised the m. p. of the *hydrate* to 88—90° (Found: N, 9·2; Cl, 11·8. $C_{17}H_{18}N_2Cl,H_2O$ requires N, 9·2; Cl, 11·6%). The *picrate* crystallised from ethyl alcohol and melted at 168—170° (Found: C, 57·8; H, 4·9. $C_{23}H_{21}O_7N_5$ requires C, 57·6; H, 4·4%).

(*b*) A mixture of *ββ*-diphenylpropionitrile (35·0 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (39·2 g.) (m. p. 122—124°; Oxley and Short, *loc. cit.*) was heated for 3 hours at 200°. After cooling, the solidified mass was recrystallised from aqueous ethyl alcohol. The yield of *toluene-p-sulphonate*, m. p. 170—174°, was 92·5% (Found: C, 68·5; H, 6·5; N, 6·7. $C_{24}H_{26}O_3N_2S$ requires C, 69·2; H, 6·2; N, 6·6%). A suspension of this salt (15·0 g.) in hot water was treated with 20% sodium hydroxide

(30 c.c.) and extracted with chloroform. After evaporation of the solvent the residue crystallised (7·6 g.). After recrystallisation from acetone, the m. p. was 102° (Found : N, 11·3%). This base (2·0 g.) in acetone (2 c.c.) was treated with 23% alcoholic hydrogen chloride solution (1·2 c.c.). Recrystallisation of the crude product from acetone gave the hydrated hydrochloride, m. p. 88—90° (Found : C, 66·9; H, 7·0; N, 9·1%), whence the base, m. p. 100·5°, could be regenerated.

Ethyl ββ-Diphenylpropionate.—This was prepared from the nitrile by application of Spiegel's method (*Ber.*, 1918, **51**, 296). Diphenylpropionitrile (8·0 g.), absolute ethyl alcohol (7 c.c.), and concentrated sulphuric acid (2·0 c.c.) were refluxed for 3 hours at 120—130° (bath). Ethyl alcohol was distilled off *in vacuo* and the residue mixed with water (100 c.c.). The oil which separated was extracted with ether, and the solution was dried and evaporated. The residue distilled from a Hickman flask at 138—141°/0·25 mm. (yield, 5·5 g.). Wislicenus and Ebie (*Ber.*, 1917, **50**, 253) gave b. p. 190—193°/12 mm.

ββ-Diphenylpropiono-2-aminoethylamide (VII).—The above ester (5·5 g.) and absolute ethylenediamine (6·0 c.c.) were heated in a sealed tube for 18 hours at 210—230°. After cooling, the excess of diamine was distilled off and the residual oil transformed (in ethyl alcohol solution) into the *hydrochloride*. Crystallisation from ethyl alcohol gave 2·0 g. of the product, m. p. 214—215° (Found : N, 9·5; Cl, 11·7. $C_{17}H_{21}ON_2Cl$ requires N, 9·2; Cl, 11·6%). From aqueous solution of this the *base* was obtained by treatment with 40% aqueous sodium hydroxide. Recrystallisation from benzene gave white prisms, m. p. 118° (Found : N, 10·6. $C_{17}H_{20}ON_2$ requires N, 10·4%).

ββ-Diphenylpropionamidine (VIII; R = H).—To a suspension of the crude imidate hydrochloride (prepared from 4·5 g. of nitrile) in absolute ethyl alcohol (10 c.c.), 8% absolute ethyl-alcoholic ammonia (100 c.c.) was added and the mixture was shaken in a closed flask for 3 hours at 20°. After 12 hours, shaking was repeated for a further 2 hours. Ammonium chloride, which separated, was filtered off and the filtrate evaporated *in vacuo* at 30—35° (bath). The residue was dissolved in chloroform (30 c.c.), the solution washed with water, 10% sodium hydroxide solution, and water, and the chloroform was distilled off. The oily residue (5·2 g.) is the crude base (VIII; R = H). The *picrate*, after recrystallisation from absolute ethyl alcohol, melted at 209—209·5° (Found : C, 55·8; H, 4·0; N, 15·5. $C_{23}H_{21}O_7N_5$ requires C, 55·6; H, 4·2; N, 15·5%).

NN-Dimethyl-ββ-diphenylpropionamidine (VIII; R = Me).—The crude imidate hydrochloride (4·5 g.) was dissolved in ethyl alcohol (20 c.c.), 18% ethyl-alcoholic dimethylamine solution (4·5 c.c.) was added and the mixture was set aside for 24 hours at room temperature. After evaporation of alcohol the residue was recrystallised from ethyl alcohol–ether. 3·2 G. of *hydrochloride*, m. p. 249°, were obtained (Found : C, 70·5; H, 7·3; N, 9·5. $C_{17}H_{21}N_2Cl$ requires C, 70·7; H, 7·3; N, 9·7%).

NN-Pentamethylene-ββ-diphenylpropionamidine (VIII; $NR_2 = N{<}(CH_2)_5$).—To the solution of crude imidate hydrochloride (6·2 g.) in absolute ethyl alcohol (30 c.c.) piperidine (2·0 g.) was added and the mixture set aside for 12 hours at room temperature. It was then evaporated *in vacuo* to dryness and gave, as above, 4·2 g. of *hydrochloride*, m. p. 250° (Found : C, 73·1; H, 7·6. $C_{20}H_{25}N_2Cl$ requires C, 73·0; H, 7·7%).

Ethyl Diphenylacetimidate Hydrochloride.—A solution of diphenylacetonitrile (6·6 g.), m. p. 74°, prepared by dehydration of diphenylacetamide (Neure, *Annalen*, 1889, **250**, 142), in a mixture of chloroform (30 c.c.) and absolute ethyl alcohol (5·0 c.c.) was saturated with hydrogen chloride at 0° and set aside for 14 days at room temperature in a closed flask. After evaporation of the solvents a crude product suitable for the preparation of the amidine was obtained.

Diphenylacetamidine (IX).—(*a*) A suspension of the above imidate hydrochloride in absolute ethyl alcohol (20 c.c.) was mixed with 8% ethyl-alcoholic ammonia (18·5 c.c.), and the mixture shaken for 2 hours at 20°. After 12 hours, shaking was repeated for an hour. Ammonium chloride was filtered off and the filtrate evaporated under reduced pressure. The remaining oil was dissolved in chloroform (50 c.c.), the solution washed with 5*N*-sodium hydroxide and water, and the chloroform evaporated. The residue is the crude amidine, m. p. 95—97° (7·1 g.). It gave a *picrate* which after recrystallisation from ethyl alcohol melted at 224—225° (decomp.) (Found : C, 54·6; H, 3·6. $C_{20}H_{17}O_7N_5$ requires C, 54·7; H, 3·9%). The hydrochloride could not be obtained crystalline.

(*b*) A mixture of diphenylacetonitrile (2·5 g.) and dried ammonium thiocyanate (4·0 g.) was heated for 5 hours at 180°. After cooling, the product was treated with hot water (10 c.c.), and the solution filtered. The filtrate was made alkaline with 5*N*-sodium hydroxide (10 c.c.) and extracted with chloroform. After evaporation of the solvent the residue gave a picrate (0·4 g.), m. p. 224—225°, identical with the above product.

2-Benzhydryl-4 : 5-dihydroglyoxaline (X).—A mixture of diphenylacetonitrile (9·6 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g.) was heated for 3 hours at 200—210°, during which ammonia was evolved. The cooled mass was extracted with hot water (500 ml.), the mixture made alkaline with 5*N*-sodium hydroxide (50 c.c.) and extracted with chloroform (200 c.c.). After drying of the solution the chloroform was evaporated off. The residue (61%) is the base, which after recrystallisation from acetone melts at 133—135° (Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 3195, gives 137°). From the base were prepared the picrate, crystallising from ethyl alcohol and melting at 184·5° (Aspinall, *loc. cit.*, gives 185°) (Found : C, 56·6; H, 4·4; N, 15·6. Calc. for $C_{23}H_{19}O_7N_5$: C, 56·9; H, 4·1; N, 15·1%), and hydrochloride, crystallising from ethyl alcohol–ether and melting at 180—182° (Ciba, Austrian P. 150,307; *Zentr.*, 1937, II, 3039, gives 192—193°) (Found : N, 10·0; Cl, 12·5. Calc. for $C_{16}H_{17}N_2Cl$: N, 10·3; Cl, 13·0%).

The authors are indebted to Mr. J. Křeček and Mrs. J. Křečková for testing the above compounds for antihistaminic activity.

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43. *The Determination of the Liquid Density of Chlorine Trifluoride.*

By A. A. Banks and A. J. Rudge.

The liquid density of chlorine trifluoride under its own vapour pressure has been determined over the range −5° to +46° in sealed Pyrex glass dilatometers. Contrary to a previous report, pure chlorine trifluoride was found to have no detectable action on dry Pyrex glass. The results are expressed in the equation $d_4^t = 1{\cdot}8853 - 2{\cdot}942 \times 10^{-3}t - 3{\cdot}79 \times 10^{-6}t^2$.

The preparation of chlorine trifluoride was first described by Ruff and Krug (*Z. anorg. Chem.*, 1930, **190**, 270), since when only nine communications (Schmitz and Schumacher, *Z. Naturforsch.*, 1947, **2a**, 362, 363; Domange and Neudorffer, *Compt. rend.*, 1948, **226**, 920; Schäfer and Wicke, *Z. Elektrochem.*, 1948, **52**, 205; Booth and Pinkston, *Chem. Reviews*, 1947, **41**, 421; B.I.O.S. Final Report No. 1595; C.I.O.S. Report No. XXII-17) dealing with this compound have appeared in the literature. Ruff and Krug determined some of the physical properties of chlorine trifluoride, but neither they nor any of the later workers have reported a value for the liquid density.

The present determinations were carried out on chlorine trifluoride which was prepared by direct combination of the elements at 280° and purified by passing the vapour over sodium fluoride pellets to remove hydrogen fluoride and then by distillation *in vacuo* to remove more volatile impurities such as chlorine and chlorine monofluoride. In the absence of a precise method of determining fluorine, chemical estimation of the purity of the chlorine trifluoride used was not undertaken.

The dilatometers were calibrated with distilled water after the measurements on chlorine trifluoride had been made; visual examination of the glass at this stage revealed no etching. In calculating the results, all weighings were reduced to vacuum, and the weight of chlorine trifluoride present as vapour was calculated by the equation

$$\log p = 7{\cdot}42 - 1{\cdot}292 \times 10^3/T$$

given by Ruff and Krug (*loc. cit.*). The density values obtained were fitted to a curve of the type $d = a + bt + ct^2$ by the method of least squares, giving the equation

$$d_4^t = 1{\cdot}8853 - 2{\cdot}942 \times 10^{-3}t - 3{\cdot}79 \times 10^{-6}t^2$$

The experimental results, together with the values calculated from the above equation, are shown in Table I. Table II gives the calculated value of the density of liquid chlorine trifluoride at regular intervals of temperature and at the boiling point. A direct determination of the boiling point has given a value of 12·0° ± 0·1° at 760 mm. of mercury pressure, which is 0·7° higher than that calculated by Ruff and Krug from their vapour-pressure measurements. The determination was carried out in a Pyrex glass apparatus in which pure chlorine trifluoride was refluxed and the condensate allowed to impinge on a thermocouple calibrated against an N.P.L. standard thermometer.

The standard deviation of the calculated values in Table I from the observed values is ±0·0003 g./ml.

Table I.

t.	*d* (obs.), g./ml.	*d* (calc.), g./ml.	*d* (obs.) − *d* (calc.), 10^{-4}.	$(\Delta d)^2$, 10^{-8}.	*t*.	*d* (obs.), g./ml.	*d* (calc.), g./ml.	*d* (obs.) − *d* (calc.), 10^{-4}.	$(\Delta d)^2$, 10^{-8}.
−4·07°	1·8970	1·8972	−2	4	26·90	1·8031	1·8034	−3	9
1·70	1·8806	1·8803	3	9	26·92	1·8036	1·8033	3	9
9·64	1·8566	1·8566	0	0	38·71	1·7654	1·7657	−3	9
12·68	1·8476	1·8474	2	4	38·77	1·7661	1·7655	6	36
20·92	1·8218	1·8221	−3	9	45·63	1·7431	1·7431	0	0
									Σ = 89

Table II.

t	0°	10°	12°	15°	20°	25°	30°	35°	40°	45°	50°	60°
d (calc.)	1·8853	1·8555	1·8500	1·8403	1·8249	1·8094	1·7936	1·7777	1·7616	1·7452	1·7287	1·6951

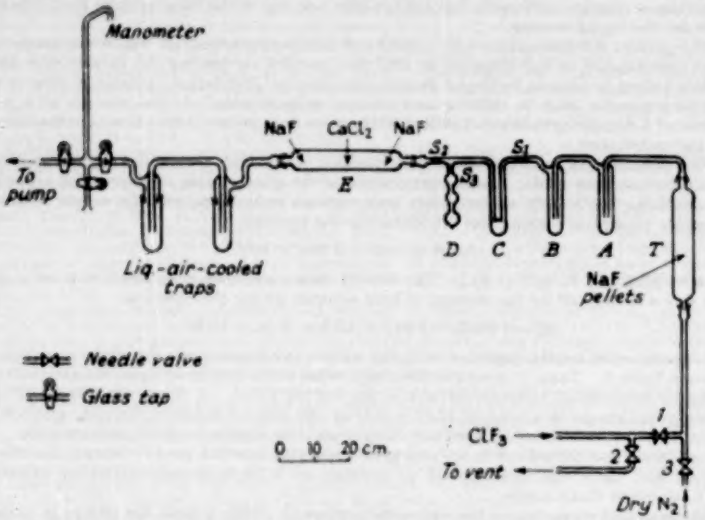
Experimental.

The apparatus used is shown diagramatically in Fig. 1. Except for the three valves (1, 2, and 3), it was constructed entirely of Pyrex glass, the cone joints being sealed with a chloro-fluoro-hydrocarbon wax which had been shown to be inert to chlorine trifluoride vapour at normal temperatures. The

valves were Negretti and Zambra needle valves which had been carefully degreased, the gland packings being replaced with asbestos string soaked in a chlorine-trifluoride-resistant chloro-fluoro-hydrocarbon oil. These valves were connected with their seatings towards the apparatus which could therefore be evacuated with the valves closed, without the need for ensuring that the glands were vacuum-tight.

The apparatus was rigorously cleaned and dried before assembly, and all the glassware was baked out in vacuo for an hour before use to ensure the complete absence of moisture. Chlorine trifluoride vapour, from a steel cylinder containing the liquid under pressure, was admitted through valve 1, and was diluted with approx. half its volume of dry nitrogen admitted through valve 3. The gas mixture was passed through the hydrogen fluoride absorption tube T packed with sodium fluoride pellets, and the chlorine trifluoride was condensed in trap B cooled in a solid carbon dioxide–trichloroethylene bath. Trap A served to collect any sodium fluoride dust blown from the pellets. When sufficient chlorine trifluoride had been collected in B, valves 1 and 3 were closed and the whole apparatus was evacuated. The low-temperature bath was transferred from B to C, and the chlorine trifluoride was distilled into C. During this distillation, any chlorine or chlorine monofluoride, together with a little chlorine trifluoride passed to the calcium chloride tube E which served to destroy the fluorides, and chlorine was collected in the traps cooled in liquid air. The trap C and dilatometer D were sealed off *in vacuo* as a unit at the constrictions S_1 and S_2.

FIG. 1.



The liquid chlorine trifluoride was allowed to warm to room temperature and, by tilting, sufficient chlorine trifluoride was poured into the dilatometer (shown in detail in Fig. 2*A*) to fill it to the required level at the temperature at which measurement was to be made. The dilatometer and trap were then simultaneously cooled in solid carbon dioxide, and the dilatometer was isolated by sealing off at S_2. During cooling of the dilatometer with the trap attached, chlorine trifluoride tended to distil from the dilatometer back to the trap because of the faster cooling of the trap with its smaller volume of liquid. To overcome this, the type of dilatometer shown in Fig. 2*B*, which permits sufficiently accurate adjustment of the quantity of chlorine trifluoride to be made at −78°, was used in the later determinations. By extrapolation of the density results already obtained, the two bulbs were made of such volumes that when the lower bulb was filled with chlorine trifluoride at −78°, the amount of chlorine trifluoride present was sufficient to fill both bulbs at the temperature at which it was intended to carry out the determination.

The thermostat used consisted of a Dewar flask with clear observation strips, filled with dry carbon tetrachloride. This liquid was used in preference to water as a safety precaution, as it had been shown to be stable to chlorine trifluoride up to at least 80°. Temperature control above room temperature was obtained by manual operation of a variable-voltage power pack supplying current at 0—15 volts to a small heating coil immersed in the carbon tetrachloride which was rapidly stirred. A maximum of 3 watts power input was required to maintain the highest temperature used. For temperatures below room temperature, cooling was effected and maintained by the addition of small pieces of solid carbon dioxide. The temperature was measured with a Beckmann thermometer calibrated against a set of N.P.L. standard thermometers. The dilatometer was supported in the thermostat by means of a rigid wire cradle in such a position that the cathetometer measurements were made through a section

of the unsilvered strip previously shown to have the minimum optical distortion. The dilatometer was maintained for ½ hour at the temperature (±0·01°) required to bring the chlorine trifluoride meniscus to the centre of one of the lengths of uniform-bore capillary tubing. The height of the meniscus above the lower tip of the dilatometer was measured using the cathetometer, and the temperature was recorded. These measurements were checked after 10 minutes to ensure that temperature equilibrium had been attained. Raising or lowering the temperature enabled a second determination to be made with the other section of uniform capillary tubing.

FIG. 2.

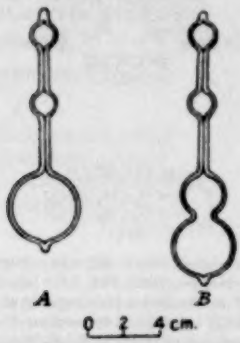


FIG. 3.

The dilatometer was dried, weighed, and then emptied using the apparatus shown in Fig. 3. The dilatometer was inserted into a rubber bung, and a scratch made at the centre of the upper measuring capillary. A sleeve of thin rubber tubing was placed over the scratch and the bulb of the dilatometer was cooled in solid carbon dioxide. The stem was broken under the sleeve, and the fragments of glass, which were retained inside the sleeve, were collected. The dilatometer was immediately inverted in the tube *A* (Fig. 3) which was cooled in solid carbon dioxide and, by means of a water-pump attached to trap *B*, the apparatus was evacuated. The bulk of the chlorine trifluoride was collected in *A*, and the remainder was condensed in trap *B* cooled in liquid air. The dilatometer was removed, rapidly rinsed with water, and then dried.

The dilatometer and glass fragments were weighed and the dilatometer was calibrated to the cut with distilled water at the temperature of the determination. The height of the cut above the tip of the dilatometer was measured with the dilatometer immersed in the thermostat, to minimise any errors due to distortion effects of the Dewar flask walls, and the bore of the capillary was measured by means of a thread of mercury. The volume of liquid chlorine trifluoride at the temperature of the determination could then be calculated. The volume of chlorine trifluoride at the lower temperature of determination was obtained in a similar manner. By a similar technique, the volume of chlorine trifluoride vapour over the liquid was determined and the weight of this vapour calculated as indicated previously.

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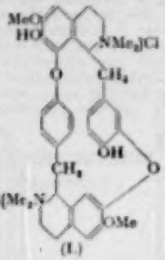
44. *Some New Curarising Agents.*

By JAMES WALKER.

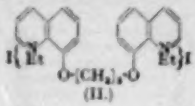
As all of the more potent of the newer curarising agents contain at least two quaternary ammonium groups separated by a chain of about ten atoms, *decamethylene*-1 : 10-*bisdimethylsulphonium di-iodide* (VI) and *decamethylene*-1-*dimethylsulphonium*-10-*trimethylammonium di-iodide* (VIII) have been prepared and examined. Both were found to be powerful curarising agents but to be less active than decamethylene-1 : 10-bistrimethylammonium di-iodide (IV). Succinoylcholine dibromide has also been studied.

ALTHOUGH the curariform activity of 'onium cations has been known for many years, none has, until recently, been known to exert an effect comparable in magnitude with that of the active constituents of native curare. The elucidation of the structure of (+)-tubocurarine chloride (I) by King (*J.*, 1935, 1381; 1939, 1157; 1948, 265) and its introduction as an adjuvant in anæsthesia (Griffith and Johnson, *Anesthesiology*, 1942, **3**, 418; Cullen, *Surgery*, 1943, **14**, 261) have, however, provided a stimulus to further search for other compounds with similar properties.

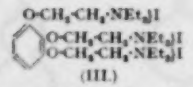
This work has been recently reviewed by Bovet and Bovet-Nitti (*Experientia*, 1948, **4**, 325; *Rend. Ist. Superiore di Sanità*, 1949, **12**, Parte I—III, *Numero speciale sui curari di sintesi*) and by Paton (*J. Pharm. Pharmacol.*, 1949, **1**, 273), and, as the earlier work relating curariform activity with chemical constitution has been reviewed by Ing (*Physiol. Rev.*, 1936, **16**, 527) and by Craig (*Chem. Reviews*, 1948, **42**, 285), it is only necessary to indicate here the trends which recent work has taken. Bisbenzylisoquinoline quaternary salts closely related to, and structurally reminiscent of, (+)-tubocurarine chloride (I) have been shown to have paralysant



(I.)



(II.)



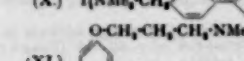
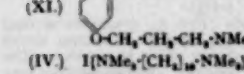
(III.)

properties similar to those of (I) (Marsh *et al.*, *J. Pharmacol.*, 1948, **92**, 454; 1948, **93**, 109; 1949, **95**, 100; *Fedr. Proc.*, 1949, **8**, 318; Collier *et al.*, *Nature*, 1948, **161**, 817; Stoelting *et al.*, *Anesthesia and Analgesia*, 1949, **28**, 130) but to possess no marked advantages over the latter. Bovet and his collaborators (*Compt. rend.*, 1946, **223**, 597) attempted to analyse the structure of (+)-tubocurarine chloride (I) and observed marked activity in 1 : 5-bis-(8-quinolyloxy)-pentane diethiodide (3381 R.P.) (II). In subsequent phases of this work, Bovet's group has examined substituted ethers, including choline ethers, of phenols and polyhydric phenols (*ibid.*, 1947, **225**, 74), among which pyrogallol trisdiethylaminoethyl ether triethiodide ("Flaxedil"), (3697 R.P.) (III) has received clinical application (Mushin *et al.*, *Lancet*, 1949, I, 726). Choline esters of dibasic aromatic acids were moderately active but their action was more transient (Bovet *et al.*, *Helv. physiol. Acta*, 1948, **6**, C52).

The most potent synthetic compound hitherto obtained was discovered independently by Barlow and Ing (*Nature*, 1948, **161**, 718; *Brit. J. Pharmacol.*, 1948, **3**, 298) and, in this Institute, by Paton and Zaimis (*Nature*, 1948, **161**, 718) in decamethylene-1 : 10-bistrimethylammonium di-iodide (C10, "Decamethonium iodide") (IV), which has already proved satisfactory in clinical use (Organe, Paton, and Zaimis, *Lancet*, 1949, I, 21; Organe, *ibid.*, p. 773; Davies and Lewis, *ibid.*, p. 775; Hewer *et al.*, *ibid.*, p. 817; Hobson and Prescott, *ibid.*, p. 819). Furthermore, higher and lower homologues were less active than (IV) and pentamethylene-1 : 5-bistrimethylammonium di-iodide (V) actually antagonises the relaxation produced by (IV) (Paton and Zaimis, *Nature*, 1948, **162**, 810; Organe, Paton, and Zaimis, *loc. cit.*). The feature common to all the more active compounds, despite certain differences in their pharmacological action, is that two quaternary ammonium groups are separated by a chain of between 8 and 12 atoms, indicating that the essential structural requirement for high activity may be that two such groups should occupy positions optimally separated in the same molecule (Barlow and Ing, *loc. cit.*; cf. also Kimura *et al.*, *J. Pharmacol.*, 1949, **95**, 149). The present communication describes several extensions of this thesis and includes sulphonium types.

Decamethylene-1 : 10- (VI) and *pentamethylene*-1 : 5-*bisdimethylsulphonium di-iodide* (VII), the sulphonium analogues of (IV) and (V), were obtained by the addition of methyl iodide to 1 : 10-*bismethylthio*-n-*decane* and 1 : 5-*bismethylthio*-n-*pentane* respectively. *Decamethylene*-1-*dimethylsulphonium*-10-*trimethylammonium di-iodide* (VIII), a hybrid of (IV) and (VI), was obtained by converting ethyl ω-bromoundecoate into *ethyl ω-methylthioundecoate* and then methylating the 10-*methylthio*-n-*decylamine hydrochloride* obtained by Curtius degradation. As the two quaternary ammonium groups in the succinic ester of choline are separated by a chain of 10 atoms, thereby complying with the above postulate, choline succinate dibromide (IX) was prepared and examined. Shortly afterwards it was learned that Bovet and his collaborators had also examined this ester (*Gazzetta*, 1949, **79**, 129; *Rend. Ist. Superiore di Sanità*, 1949, **12**, 106), and the appearance of a note by Phillips (*J. Amer. Chem. Soc.*, 1949, **71**, 3264) on aliphatic dicarboxylic acid aminoethyl ester alkyl iodides is a further indication of the interest aroused in purely aliphatic compounds by the work of Paton and Zaimis (*locc. cit.*). It should be noted

in passing that (IX) may be considered as being derived by linking two molecules of acetylcholine through the acetyl groups by the removal of two hydrogen atoms. Although the distance

	Compound.	Rabbit " head-drop " dose (mg./kg.).	Mean relative molecular activities.*
(VI.)	$I(SMe_2\cdot[CH_2]_{10}\cdot SMe_2)I$	1·7	6·5
(VII.)	$I(SMe_2\cdot[CH_2]_6\cdot SMe_2)I$	>38	—
(VIII)	$I(SMe_2\cdot[CH_2]_{10}\cdot NMe_2)I$	0·35	31·6
(IX.)	$CH_3\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NMe_2)Br$ $CH_3\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NMe_2)Br$	0·15—0·25	48·3
(X.)		1·53	7·8
(XI.)		0·47	27·0
(IV.)	$I(NMe_2\cdot[CH_2]_{10}\cdot NMe_2)I$	0·10—0·12	100
(I.)	(+)-Tubocurarine chloride	0·22—0·23	74·0
(III.)	" Flaxedil "	0·5	38·3

* Expressed as percentage of the activity of (IV).

between the two quaternary ammonium groups in (I) is fixed by stereochemical considerations, the separation of the two charged groups in the aliphatic and mixed aromatic–aliphatic types is not uniquely determined, apart from the fact that the two charged groups will be mutually repulsive. As an example of a rigid structure, *4 : 4'-bis(dimethylaminomethyl)diphenyl dimethiodide* (X) was prepared, since, in this substance, the fourteen carbon atoms forming the " backbone " of the molecule are coplanar; the compound, however, was found to be less active than (I), (IV), or (IX). *1 : 4-Bis-(3-dimethylaminopropoxy)benzene dimethiodide* (XI), obtained by methylation of the corresponding *diprimary amine hydrochloride*, is a higher homologue of the choline ethers of quinol studied by Bovet and his colleagues (*Compt. rend.*, 1947, **225**, 74). The compounds described in the present communication were kindly tested by Dr. W. D. M. Paton and Dr. E. J. Zaimis using the rabbit " head-drop " technique, and the results are recorded above. It is noteworthy that the decline in activity in passing from (IV) to (VIII) and (VI) closely parallels the observations of Ing and Wright (*Proc. Roy. Soc.*, 1933, *B*, **114**, 48) on the relative activities of the tetramethylammonium and trimethylsulphonium ions.

Experimental.

Decamethylene-1 : 10-diisothiourea Dihydrobromide.—A solution of decamethylene dibromide (15 g.) and thiourea (7·6 g.) in alcohol (150 c.c.) was refluxed until a test drop of the solution no longer gave a dark precipitate with ammoniacal silver nitrate, about 5 hours being required. The *dihydrobromide* separated from alcohol in clusters of colourless, rectangular plates, m. p. 160—161° (Found: N, 12·7. $C_{12}H_{28}N_4S_2.2HBr$ requires N, 12·4%). The yield was quantitative.

1 : 10-Bismethylthio-n-decane.—The foregoing dihydrobromide (20 g.) was dissolved in *N*-sodium hydroxide solution (180 c.c.) with gentle warming on the water-bath, and the small amount of oil which separated was taken into solution by addition of a further small volume of alkali. The cold, filtered, alkaline solution was shaken with methyl iodide (5·6 c.c., 2 mols.) for 3 hours and the resulting oil was extracted with ether, washed with aqueous sodium hydroxide, dried, and recovered (9·64 g.). Distillation afforded the *bismethylthio*-compound as a colourless, mobile oil (8·3 g.), b. p. 195—196°/16 mm., n_D^{20} 1·4946 (Found: C, 61·3; H, 11·1. $C_{12}H_{26}S_2$ requires C, 61·5; H, 11·1%).

Decamethylene-1 : 10-bisdimethylsulphonium Di-iodide (VI).—The preceding bisthioether (7·1 g.) was treated with methyl iodide (4 c.c.) and methyl alcohol (2 c.c.) was added. The mixture gradually became viscous when kept at room temperature and solidified on scratching after 2½ days. The *di-iodide* separated from methyl alcohol–ethyl acetate (1 : 1·5) in small, stout, colourless prisms (12·3 g.), m. p. 119—120° (effervescence) (Found: C, 32·7; H, 6·2. $C_{14}H_{32}S_2I_2$ requires C, 32·4; H, 6·2%).

1 : 5-Bismethylthio-n-pentane.—A solution of pentamethylene dibromide (11·2 g.) and thiourea (7·6 g.) in alcohol (100 c.c.) was refluxed until all the thiourea had reacted; on removal of the solvent the residue crystallised. The crude bisthiuronium bromide was decomposed with 10% aqueous sodium hydroxide solution (120 c.c.) in the manner described above, and the filtrate was shaken for 3 hours with methyl iodide (6·6 c.c.). The *bismethylthio*-compound was a colourless oil (4·8 g.), b. p. 128°/22 mm., n_D^{20} 1·5103 (Found: C, 51·4; H, 10·2. $C_7H_{16}S_2$ requires C, 51·2; H, 9·8%).

Pentamethylene-1 : 5-bisdimethylsulphonium Di-iodide (VII).—The preceding bisthioether (3·5 g.), methyl iodide (3 c.c.), and methyl alcohol (3 c.c.) were mixed and kept at 37° for 48 hours, the product crystallising out. The *di-iodide* separated from alcohol in colourless, fern-like masses, m. p. 182—183° (effervescence) (Found: C, 24·3; H, 5·0. $C_9H_{22}S_2I_2$ requires C, 24·1; H, 4·9%).

Ethyl ω-Methylthioundecoate.—ω-Bromoundecoic acid (Ashton and Smith, *J.*, 1934, 1308) is conveniently esterified with only one-fifth of the proportions of alcohol and concentrated sulphuric acid recommended by Walker and Lumsden (*J.*, 1901, **79**, 1196). ω-Carbethoxyundecylisothiourea hydrobromide (26·1 g.), prepared from equimolecular amounts of ethyl ω-bromoundecoate and thiourea in the usual manner, was dissolved in alcohol (80 c.c.) and treated with alcoholic sodium ethoxide (from 1·63 g. of sodium and 25 c.c. of alcohol). After 2 hours at room temperature a further equivalent of alcoholic sodium ethoxide was added. The filtered solution was then treated with methyl iodide (4·7 c.c.); heat was evolved, and the mixture was left at room temperature overnight. The alcohol was removed by distillation, and the *ethyl* ester, recovered in ether, washed, dried, and distilled, was a colourless oil (17·8 g.), b. p. 199—200°/18 mm., n_D^{20} 1·4608 (Found : C, 64·8; H, 10·7. $C_{14}H_{28}O_2S$ requires C, 64·6; H, 10·8%).

Free ω-methylthioundecoic acid, obtained by alkaline hydrolysis of the ester, was a waxy solid and could not be recrystallised easily. The *benzamidine* salt separated from 25% alcohol in colourless, microscopic plates, m. p. 191—192° (Found : C, 65·1; H, 9·0; N, 7·9. $C_{18}H_{34}O_2S,C_7H_8N_2$ requires C, 64·8; H, 9·1; N, 8·0%).

The *hydrazide*, obtained by refluxing the ester with a slight excess of 90% hydrazine hydrate in *n*-propyl alcohol for 5 hours, separated from that solvent in fine, colourless needles, m. p. 88—89° (Found : C, 58·9; H, 10·4; N, 11·7. $C_{12}H_{26}ON_2S$ requires C, 58·5; H, 10·6; N, 11·4%).

10-*Methylthio-n-decylamine Hydrochloride.*—The preceding hydrazide (10·5 g., crude) in alcohol (200 c.c.) was treated in a freezing mixture with a concentrated aqueous solution of sodium nitrite (2·6 g.), and concentrated hydrochloric acid (6 c.c.) was added dropwise during about 40 minutes. The mixture was then diluted with ice-water (800 c.c.) and extracted with benzene. The washed benzene extract was dried and warmed slowly on the water-bath and finally boiled for 15 minutes. Most of the benzene was then distilled off and the residue was treated with concentrated hydrochloric acid (25 c.c.) and warmed on the water-bath for a short time. The acid solution was diluted with water, extracted with ether, made strongly alkaline with sodium hydroxide, and again extracted with ether. The resulting oily base (4·9 g.) was treated with excess of alcoholic hydrogen chloride and the alcohol was distilled off. The *hydrochloride* separated from ethyl acetate, or from a small volume of water, in rosettes of small, colourless plates, m. p. 160—161° (Found : C, 55·1; H, 10·6; N, 5·9. $C_{11}H_{25}NS,HCl$ requires C, 55·1; H, 10·9; N, 5·8%).

Decamethylene-1-dimethylsulphonium-10-trimethylammonium Di-iodide (VIII).—A solution of the preceding hydrochloride (1·2 g.) and sodium hydroxide (1·32 g.) in methyl alcohol (20 c.c.) was refluxed with methyl iodide (3 c.c.) for 7 hours. The neutral solution was filtered from sodium chloride and exhaustively evaporated to dryness with absolute alcohol. The residue was treated with warm acetone to dissolve the sodium iodide and the insoluble product (2·53 g.) was collected and washed with cold acetone. The *di-iodide* separated from absolute alcohol in clusters of colourless plates, m. p. 136—137° (effervescence) (Found : C, 34·7; H, 7·0; N, 2·6. $C_{16}H_{38}NSI_2$ requires C, 34·9; H, 6·9; N, 2·7%).

Di-2-bromoethyl Succinate.—A mixture of ethylene bromohydrin (35·2 c.c.), succinic acid (23·6 g.), benzene (80 c.c.), and concentrated sulphuric acid (1 c.c.) was refluxed for 12 hours on the water-bath. The mixture was diluted with ether and water, and the upper layer was thoroughly washed with sodium hydrogen carbonate solution, dried, and fractionated. The compound was obtained as a pale yellow oil (37 g.), b. p. 169°/3 mm., n_D^{20} 1·5023, crystallising on immersion in a freezing mixture (Found : C, 28·9; H, 3·9. Calc. for $C_8H_{14}O_4Br_2$: C, 28·9; H, 3·6%). Glick (*J. Biol. Chem.*, 1941, **137**, 357) records b. p. 216—217°/26 mm., and Fusco *et al.* (*Gazzetta*, 1949, **79**, 139) record b. p. 150°/1—2 mm.

Succinoylcholine Dibromide (IX).—A mixture of the above ester (25 g.), benzene (18 c.c.), and trimethylamine (9 g.) was heated in a sealed tube at 90° for 8 hours. After cooling, the upper layer of benzene was decanted and the residual gum was triturated with alcohol. The resulting white powder (17·3 g.) was collected, washed with alcohol and dried. The substance separated from absolute alcohol as a colourless, microcrystalline powder, m. p. 211° (Found : C, 37·1; H, 6·4; N, 6·4. Calc. for $C_{14}H_{30}O_4N_2Br_2$: C, 37·4; H, 6·7; N, 6·2%). Fusco *et al.* (*loc. cit.*) record m. p. 219° but no analytical data for this salt, and Glick (*loc. cit.*) records a bromine determination but no m. p.

4 : 4'-*Bis(aminomethyl)diphenyl Dihydrochloride.*—4 : 4'-Dicyanodiphenyl (23·5 g.) was reduced in methyl-alcoholic ammonia (630 c.c.; 12%) in the presence of Raney nickel (5 g.) with hydrogen at 60 atm. The mixture was warmed to about 65° and reduction was complete in about 2 hours. The catalyst was filtered off, and the solvent removed by distillation, leaving a brown syrup. The crude base was dissolved in excess of 2*N*-hydrochloric acid, and the solution, treated with charcoal, was concentrated to saturation at the b. p. On cooling, the dihydrochloride crystallised in colourless thin, transparent, rectangular plates (21·3 g.), m. p. above 350° (Found : C, 59·2; H, 6·5; N, 9·9. Calc. for $C_{14}H_{18}N_2,2HCl$: C, 59·0; H, 6·3; N, 9·8%). The observation by Albert *et al.* (*J.*, 1947, 1454) that the crystals of this salt acquire a blue tint on exposure to light was confirmed.

4 : 4'-*Bis(dimethylaminomethyl)diphenyl Dimethiodide* (X).—The preceding dihydrochloride (2·85 g.) was treated with sodium hydroxide (3·6 g.) and methyl iodide (7 c.c.) in methyl alcohol (60 c.c.) under reflux for 6 hours. The alcohol was distilled off and the residue was crystallised from water, the *dimethiodide* separating in fine colourless needles (4·8 g.), m. p. above 350° (Found : C, 43·4; H, 5·6; N, 4·8. $C_{18}H_{26}N_2I_2$ requires C, 43·3; H, 5·4; N, 5·1%). The crystals of this salt also acquired a blue tint on exposure to light.

1 : 4-*Di-(3-aminopropoxy)benzene Dihydrochloride.*—1 : 4-Di-(2-cyanoethoxy)benzene (22 g.) (Cook and Reed, *J.*, 1945, 920) was reduced in alcoholic ammonia (500 c.c.; 10%) in the presence of Raney nickel (7 g.) with hydrogen at 20 atm. The catalyst was removed, and the solvent and ammonia were distilled off. The residue was taken up in excess of 2*N*-hydrochloric acid (charcoal) and the solution was concentrated, affording a crystalline solid (21·1 g.). The *dihydrochloride* separated from 70% alcohol in clusters of colourless, irregular plates, m. p. 313—314° (Found : C, 48·6; H, 7·5; N, 9·2. $C_{12}H_{20}O_2N_2,2HCl$ requires C, 48·5; H, 7·4; N, 9·4%).

1 : 4-*Bis-(3-dimethylaminopropoxy)benzene Dimethiodide* (XI).—A solution of the preceding dihydrochloride (3 g.) and sodium hydroxide (3·6 g.) in methyl alcohol (50 c.c.) was refluxed with methyl iodide

(6·2 c.c.) for 6 hours. The solid (6·8 g.) which separated from the reaction mixture consisted of the product mixed with sodium chloride. Recrystallisation from alcohol afforded the pure *dimethiodide* in the form of sheaves of colourless needles (5·3 g.), which effloresced on drying, m. p. 267° (Found: C, 36·8; H, 6·5; loss at 100°/vac., 4·5, 4·6. Found, on material dried at 100°/vac.: C, 38·1; H, 6·3; N, 4·8. $C_{15}H_{34}O_2N_2I_2,1\frac{1}{2}H_2O$ requires C, 36·5; H, 6·3; H_2O, 4·6%. $C_{15}H_{34}O_2N_2I_2$ requires C, 38·2; H, 6·0; N, 5·0%).

The author is indebted to Drs. W. D. M. Paton and E. J. Zaimis for undertaking the biological tests, and to Mr. W. A. L. Marshment for assistance in the preparation of starting materials.

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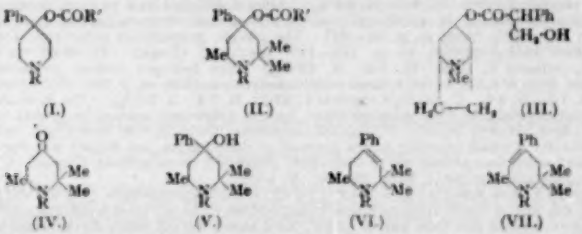
45. *The Synthesis of Piperidine Derivatives. Part IV. 4-Phenylpiperidols.*

By G. M. BADGER, J. W. COOK, and G. M. S. DONALD.

Attempts to prepare 4-acyloxy-4-phenyl-2 : 2 : 6-trimethyl-1-alkylpiperidines (II) are described. Phenylmagnesium bromide reacted with 2 : 2 : 6-trimethyl-4-piperidone to give 4-*hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine*, which readily gave the *N*-methyl derivative. Both compounds were dehydrated to the tetrahydropyridines with great facility, a circumstance which has frustrated the preparation of *O*-acyl and *O*-alkyl derivatives.

THE introduction by Eisleb and Schaumann (*Deut. med. Wochenschr.*, 1939, **65**, 967) of ethyl 4-phenyl-1-methylpiperidine-4-carboxylate ("Pethidine") as an analgesic of considerable potency has stimulated the examination of many new piperidine derivatives. The objective of such work is to prepare not only compounds of greater potency, but also those having no tendency to produce tolerance, drug addiction, and other undesirable side-effects which are characteristic of morphine and some of its derivatives. Although several highly active synthetic analgesics have been obtained it is evident, as a result of the wide clinical use of two of them ("Pethidine," "Amidone") that the problem of drug addiction has not been solved (see Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 349).

An interesting series of compounds (type I) has been described by Jensen and Lundquist (*Dansk. Tidsskr. Farm.*, 1943, **17**, 173) and by Ziering, Berger, Heineman, and Lee (*J. Org. Chem.*, 1947, **12**, 894). They were obtained by the action of arylmagnesium halides on 1-alkyl-4-piperidones to give carbinols which were esterified with a variety of acids. One of these



(I; R = Me, R' = Et) was shown to have three times the analgesic activity of morphine in the experimental animal. The importance of configuration of the molecule was shown by examination of a further series of compounds similarly obtained from 1 : 3-dimethyl-4-piperidone (Ziering and Lee, *ibid.*, p. 911). The present communication is concerned with attempts to prepare related compounds (of type II) which are related to the natural antispasmodic atropine (III) in the same sort of way that the eucaines are related to cocaine.

2 : 2 : 6-Trimethyl-4-piperidone (vinyldiacetonamine) (IV; R = H) is readily obtained by condensation of diacetonamine (4-amino-4-methylpentan-2-one) and acetal (B.P. 101,738), and on treatment with phenylmagnesium bromide gave the desired 4-*hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine* (V; R = H). This compound is dimorphic, and has m. p.s 91° and 96°. It was characterised as the *hydrochloride*, *hydrogen oxalate*, *picrate*, and *acetate*.

1 : 2 : 2 : 6-Tetramethyl-4-piperidone (*N*-methylvinyldiacetonamine) (IV; R = Me) is not

readily available, however, as it cannot be obtained by direct methylation of (IV; R = H) On the other hand, the carbinol corresponding to (IV), namely, 4-hydroxy-2 : 2 : 6-trimethylpiperidine, is easily *N*-methylated directly. As expected, therefore, *N*-methylation of the hydroxy-phenyltrimethylpiperidine (V; R = H) proceeded without difficulty, to give *4-hydroxy-4-phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine* (V; R = Me), characterised as the *hydrochloride* and *picrate*.

Both carbinols (V; R = H and Me) were readily dehydrated by warming them with alcoholic hydrogen chloride, to give *4-phenyl*-2 : 2 : 6-*trimethyl*- (VI or VII; R = H) and *4-phenyl*-1 : 2 : 2 : 6-*tetramethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine hydrochloride* (VI or VII; R = Me). Indeed, the dehydration was effected with such facility as to render the preparation of *O*-acyl and *O*-alkyl derivatives difficult or impossible, and for this reason attempts to obtain esters of type (II; R = Me) had to be abandoned.

When the magnesium complex from 2 : 2 : 6-trimethyl-4-piperidone and phenylmagnesium bromide was treated with acetic anhydride, the product consisted of a mixture of hydroxyphenyltrimethylpiperidine (V; R = H), phenyltrimethyltetrahydropyridine (VI or VII; R = H), and, curiously, *4-acetoxy-4-phenyl*-2 : 2 : 6-*trimethylpiperidine acetate* (acetate of II; R = H, R′ = Me), which was also characterised as the *hydrochloride*. The formation of this acetate is interesting, as it is evidently formed during distillation, by partial decomposition of acetoxyphenyltrimethylpiperidine with liberation of free acetic acid which then combines with another molecule of acetoxyphenyltrimethylpiperidine, to give the salt. Direct acetylation of hydroxyphenyltrimethylpiperidine (V; R = H), with acetic anhydride, gave *4-hydroxy-1-acetyl-4-phenyl*-2 : 2 : 6-*trimethylpiperidine*, together with unsaturated material (VI or VII). In the *N*-methyl series, the dehydration was found to be equally ready: under mild conditions, no reaction occurred, while under more vigorous conditions the base underwent almost complete dehydration. This resistance to acetylation is curious, as earlier workers experienced little difficulty in the preparation of compounds of type (I).

Experimental.

4-Hydroxy-4-phenyl-2 : 2 : 6-*trimethylpiperidine* (V; R = H).—To a Grignard solution (50% excess) prepared from bromobenzene (66·8 g.), magnesium (10·2 g.), and anhydrous ether (150 c.c.), 2 : 2 : 6-trimethyl-4-piperidone (20 g.; B.P. 101,738) in ether (25 c.c.) was added dropwise, with stirring. When the vigorous reaction had subsided, the solution was refluxed for a further hour, cooled, and then decomposed with ice and ammonium chloride. After being kept overnight the solid was collected, dried, extracted with ether to remove ether-soluble products, and recrystallised from ethanol–ether. Basification with sodium hydroxide, and extraction with ether, gave *4-hydroxy-4-phenyl*-2 : 2 : 6-*trimethylpiperidine* (13 g.) as colourless needles, m. p. 91—92°, from light petroleum (Found: C, 76·7; H, 9·9; N, 6·6. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6; N, 6·4%). After distillation in a vacuum, it was obtained in the form of colourless prisms, m. p. 96—97°, which on repeated recrystallisation from light petroleum, reverted to the needle form, m. p. 91—92°. The *picrate*, prepared in ether and recrystallised from water, formed yellow prisms, m. p. 188—189° (decomp.) (Found: C, 53·6; H, 5·4; N, 12·8. $C_{20}H_{24}O_8N_4$ requires C, 53·6; H, 5·4; N, 12·5%). The *hydrogen oxalate*, prepared in ether and recrystallised from ethanol–ether, formed small colourless needles, m. p. 201—202° (decomp.) (Found: C, 62·2; H, 7·5; N, 4·8. $C_{16}H_{23}O_5N$ requires C, 62·1; H, 7·4; N, 4·5%). The *hydrochloride*, prepared in ether, and crystallised from ethanol–ether, formed colourless prisms, m. p. 247—248° (decomp.) (Found: C, 65·8; H, 8·5; N, 5·7. $C_{14}H_{22}ONCl$ requires C, 65·7; H, 8·6; N, 5·5%). In the preparation of this derivative a small quantity of the product of dehydration (see below) was also isolated. The *acetate* formed colourless prisms, m. p. 223—224° (decomp.), from acetone (Found: C, 69·2; H, 8·9; N, 5·2. $C_{16}H_{25}O_2N$ requires C, 68·8; H, 9·0; N, 5·0%).

4-Phenyl-2 : 2 : 6-*trimethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine* (VI or VII; R = H).—A solution of the above hydroxyphenyltrimethylpiperidine (1·75 g.) in ethanol (15 c.c.) was saturated with hydrogen chloride and then heated to 80°, for 6 hours, during which the solution was periodically re-saturated with hydrogen chloride. The solution was then cooled, basified with dilute sodium hydroxide solution, and extracted with ether. Evaporation gave a brown oil, b. p. 90—95°/0·5 mm. (1·5 g.); the pale yellow distillate darkened on storage. *4-Phenyl*-2 : 2 : 6-*trimethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine hydrochloride*, prepared from the base in ethereal solution, formed colourless prisms, m. p. 266—267° (decomp.), from ethanol–ether (Found: C, 70·6; H, 8·3; N, 6·1. $C_{14}H_{20}NCl$ requires C, 70·8; H, 8·4; N, 5·9%). The *hydrogen oxalate* recrystallised from ethanol–ether in small colourless needles, m. p. 207—208° (decomp.) (Found: C, 65·8; H, 6·9; N, 5·1. $C_{16}H_{21}O_4N$ requires C, 66·0; H, 7·2; N, 4·8%).

4-Acetoxy-4-phenyl-2 : 2 : 6-*trimethylpiperidine*.—2 : 2 : 6-Trimethyl-4-piperidone (5 g.) was treated with a 50% excess of phenylmagnesium bromide, as above, and the solution heated under reflux for 13 hours. Acetic anhydride (11 g.), in ether, was added to the cooled solution, which was then refluxed for a further 9 hours, cooled, and hydrolysed with ice and 6*N*-hydrochloric acid. The aqueous layer was separated, basified, and extracted with chloroform. Distillation of the residue gave 2 : 2 : 6-trimethyl-4-piperidone (0·7 g.) and a yellow oil (0·3 g.), b. p. 110—130°/2 mm. When the oil was set aside, a small amount of crystals separated and on recrystallisation from ethanol–ether gave *4-acetoxy-4-phenyl*-2 : 2 : 6-*trimethylpiperidine acetate* as colourless prisms, m. p. 176—177° (Found: C, 67·1; H, 8·1; N, 4·6. $C_{18}H_{27}O_4N$

requires C, 67·3; H, 8·4; N, 4·4%). *4-Acetoxy-4-phenyl-2 : 2 : 6-trimethylpiperidine hydrochloride*, obtained in the usual way from the above acetate, formed colourless prisms, m. p. 238—239° (decomp.), from ethanol–ether (Found : C, 64·3; H, 7·9; N, 4·8. $C_{15}H_{22}O_2NCl$ requires C, 64·5; H, 8·1; N, 4·7%). The residual oil from the distillate was dissolved in ether and treated with hydrogen chloride. Crystallisation from ethanol–ether gave colourless prisms, m. p. 264—265° (decomp.), of 4-phenyl-2 : 2 : 6-trimethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine hydrochloride, identified by direct comparison with a specimen prepared as above, and also by analysis (Found : C, 70·9; H, 8·3; N, 5·4%).

Direct acetylation of 4-hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine (1 g.) by refluxing it with acetic anhydride (5 g.) for 5 minutes, followed by basification and extraction with chloroform, gave a colourless solid. After being washed with dilute hydrochloric acid to remove basic material, and recrystallised from light petroleum, *4-hydroxy-1-acetyl-4-phenyl-2 : 2 : 6-trimethylpiperidine* was obtained as colourless needles, m. p. 112—113° (Found : C, 73·2; H, 8·8; N, 5·1. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%).

4-Hydroxy-4-phenyl-1 : 2 : 2 : 6-tetramethylpiperidine (V; R = Me).—A mixture of 4-hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine (2 g.), and 40% aqueous formaldehyde (2 g.) was heated to 100°. After an hour, a vigorous reaction occurred, and the whole mass solidified. The solid was washed free from formaldehyde with water and recrystallised from light petroleum. *4-Hydroxy-4-phenyl-1 : 2 : 2 : 6-tetramethylpiperidine* (2 g.) formed colourless needles, m. p. 133—134° (Found : C, 77·4; H, 9·7; N, 6·2. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9; N, 6·0%). The *hydrochloride*, prepared in ether and recrystallised from ethanol–ether, formed colourless prisms, m. p. 243—244° (decomp.) (Found : C, 66·6; H, 8·9; N, 5·4. $C_{15}H_{24}ONCl$ requires C, 66·8; H, 8·9; N, 5·2%).

Attempted Acetylation of 4-Hydroxy-4-phenyl-1 : 2 : 2 : 6-tetramethylpiperidine.—The esterification of carbinols of similar structure was reported by Jensen and Lundquist (*loc. cit.*), and by Ziering *et al.* (*loc. cit.* and *J. Org. Chem.*, 1947, **12**, 904). Their methods have been used and extended in attempts to acetylate 4-hydroxy-4-phenyl-1 : 2 : 2 : 6-tetramethylpiperidine, but without avail. Thus, treatment with acetyl chloride in the cold, with or without an inert solvent (ether, benzene) resulted in complete dehydration to (VI or VII; R = Me) within 48 hours. Acetic anhydride under similar conditions did not react, and heating at 100° or boiling under reflux with acetic anhydride and sodium acetate, pyridine, or a trace of concentrated sulphuric acid caused dehydration in varying degrees.

An unsuccessful attempt was also made to achieve acetylation by treatment with ethylmagnesium bromide, followed by reaction of the resulting magnesium complex with cold acetic anhydride (Houben, *Ber.*, 1906, **39**, 1736).

4-Phenyl-1 : 2 : 2 : 6-tetramethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine (VI or VII; R = Me).—A solution of the above hydroxyphenyltetramethylpiperidine (0·5 g.) in ethanol (10 c.c.) was saturated with hydrogen chloride and heated to 80° for 7 hours, during which the solution was periodically re-saturated with hydrogen chloride. Basification with sodium hydroxide, and extraction with ether, gave a brown oil. *4-Phenyl-1 : 2 : 2 : 6-tetramethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine picrate* was prepared from this oil in ethanol and, after recrystallisation from ethanol formed yellow needles, m. p. 161—162° (decomp.) (Found : C, 57·5; H, 5·4; N, 12·6. $C_{21}H_{24}O_7N_4$ requires C, 57·6; H, 5·4; N, 12·6%).

One of us (G. M. B.) has held an I.C.I. Research Fellowship during this work, and we also thank the Department of Scientific and Industrial Research for a Maintenance Allowance (to G. M. S. D.). Microanalyses have been carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

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46. *The Automatic Recording of Freezing-point Curves.*

By E. F. G. HERINGTON and R. HANDLEY.

The methods in general use for securing adequate mixing of the solid and liquid during the determination of purity by the freezing-point method are reviewed, and modifications of technique are described which avoid some of the difficulties inherent in the current procedures.

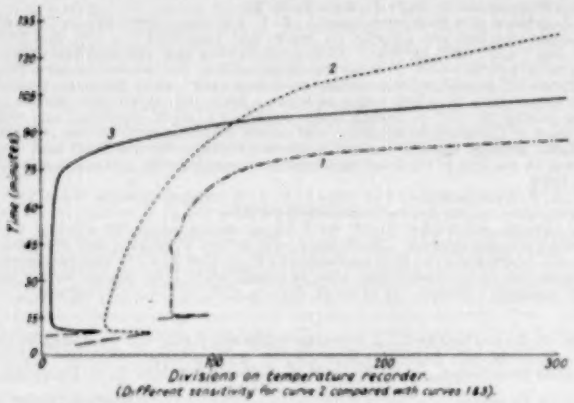
RECORDS of the variation of temperature with time obtained during the freezing of a liquid are now widely used as the basis of a test for chemical purity. The conditions under which such curves can be employed to determine the impurity in a given sample have been discussed by a number of investigators (White, *J. Physical Chem.*, 1920, **24**, 393; Mair, Glasgow, and Rossini, *J. Res. Nat. Bur. Stand.*, 1941, **26**, 591; Taylor and Rossini, *ibid.*, 1944, **32**, 1947; Glasgow, Streiff, and Rossini, *ibid.*, 1945, **35**, 355; Stull, *Ind. Eng. Chem., Anal.*, 1946, **18**, 234; Schwab and Wichers, "Temperature, its measurement and control in science and industry," p. 256; Glasgow, Beadle, Axilrod, and Rossini, *Ind. Eng. Chem., Anal.*, 1948, **20**, 460).

Essential conditions for the application of the freezing-point method are the maintenance of thermodynamic equilibrium between the liquid and crystallised solid while heat is withdrawn from the system at a controlled rate. These conditions are usually maintained by stirring vigorously and by using a cooling bath some 80° lower in temperature than the freezing point of the sample under investigation. The rate of cooling is selected by varying the gas pressure

in the jacket surrounding the specimen during the preliminary cooling. The temperature of the solid–liquid system can be measured by means of a platinum resistance thermometer and the time–temperature curve can be obtained manually but this method is so laborious that Stull (*loc. cit.*) has developed an automatic temperature recorder which is activated by a small platinum resistance thermometer. We have recently described an apparatus for recording temperature changes which makes use of a thermistor as the temperature-sensitive element (Herington and Handley, *J. Sci. Inst.*, **1948**, **25**, 434). For any desired temperature sensitivity a more robust recorder can be used with a thermistor than is required by a platinum resistance thermometer, and moreover the heat capacity of a thermistor is very small. The advantages of using small thermometers of low heat capacity in the freezing-curve technique were recognised early in the history of the subject by White (*loc. cit.*).

Various types of motor-driven stirrers which may be used in the freezing-point apparatus have been described by Rossini *et al.* (*loc. cit.*) but these all cease to operate when only a fraction of the liquid has frozen. This failure of the stirrer affects the rate of cooling and as a result a change of direction in the curve suddenly appears at the point where the stirrer stops (see

FIG. 1.



Curve 1.—*Obtained with mechanical stirrer.*
Curves 2 *and* 3.—*Obtained with apparatus described in this paper.*

Fig. 1, curve 1). Inspection of curves obtained by other observers reveals that this behaviour is common and is not peculiar to the mechanically-stirred equipment which we used at the outset of our work. In motor-stirred apparatus the liquid is usually protected from contact with atmospheric moisture by the passage over the liquid surface of a stream of purified air which is allowed to escape through the gland around the shaft of the stirrer.

An alternative method for securing mixing and preventing contact with moist air is to use a sealed-in stirrer operated by a solenoid (Stull, *loc. cit.*), but in this case also the stirrer stops at rather an early stage during the freezing and it is necessary to ensure that no electrical interference is produced in the temperature-measuring circuit by the current in the solenoid.

Schwab and Wichers (*loc. cit.*) have sought to overcome these difficulties by employing a stream of gas bubbles introduced into the liquid through a fine sintered-glass diaphragm. This method has much to recommend it but is not particularly suitable for work when a large number of compounds is to be examined, because of the difficulty of cleaning and drying the sintered-glass plates.

In the apparatus we describe, adequate mixing has been obtained by applying a pulsating gas pressure to the liquid surface in such a way as to produce oscillations in a U-shaped column of the liquid being frozen. Thus mixing of the liquid phase continues until practically all the specimen has frozen while at the same time the material is kept out of contact with moist air. The apparatus is easily cleaned and only 10 c.c. of liquid are required for a determination of the freezing-point curve.

Experimental.

The temperature-recording equipment and the freezing-point apparatus will be discussed separately although they are in fact interdependent units.

Recording of Temperature Changes.—The thermometric equipment used was similar to that described previously as suitable for temperatures from −40° to 140° (Herington and Handley, *loc. cit.*), except that a Tinsley D.C. amplifier and pen recording millivolt-meter have replaced the photographically-recording galvanometer. A constant-voltage transformer smooths the input to the amplifier. The amplifier and recorder have two sensitivity ranges corresponding to 5 and 20 mv. for a full-scale deflection on the chart. A less sensitive galvanometer has been incorporated in the circuit to assist in the preliminary balancing of the bridge and press-button switch-gear has been used so that the out-of-balance current of the bridge can be fed to the recorder or galvanometer at will.

As an indication of the sensitivity which can now be obtained it has been established that a full-scale deflection of 100 divisions (3½ in.) is equal to a difference of 0·24° for temperatures around 5·8° with use of the 5-mv. range on the recorder and a thermistor of approx. 2000 ohms resistance at room temperature when there is an E.M.F. of 4 volts across the bridge.

Thermistors can be used at temperatures as low as −130° and may thus be employed, for example, to study the freezing-point characteristics of samples of *n*-pentane. We are indebted to Messrs. Standard Telephones and Cables Ltd. for a special type F thermistor having a resistance at room temperature of 200 ohms which increases to approx. 2·5 megohms at −130°. A sensitivity of 0·62° per 100-divisions deflection of the recorder pen at −130° has been obtained by using this thermistor as part of one of the variable arms of a bridge of 11 megohms with two ratio arms of 1 megohm each, and with 120 volts from a dry battery applied across the bridge.

Vapour-pressure thermometers constructed according to the design of Stock (*Z. Electrochem.*, 1923, **29**, 354), but with an additional pocket for the thermistor, may be used for the calibration of thermistors at low temperatures. The temperature during the calibration must be allowed to fall slowly in order to avoid difficulties which may arise from the different speeds of response of the two temperature-sensitive elements.

Freezing-point Apparatus.—The dimensions of the apparatus are of some importance and are indicated in Fig. 2 which is drawn to scale. A fluctuating gas pressure is produced in the gas line *F* by means of the pulsing meter *E*. The construction of this meter and its use in another connection have been described in a communication from this laboratory (Preston and Worthington, *Chem. and Ind.*, 1947, p. 612). Compressed air for working the meter has been obtained from a large compressor delivering gas at 20 lbs. per sq. in., but we have established that a satisfactory source is an ordinary small rotating blower of the type commonly used by glass blowers. The air stream causes the pressure to rise in the gas line *F* until the mercury is driven over the narrow loop in *E*, and then the pressure in *F* suddenly drops. These pressure fluctuations set up oscillations of the liquid in the U tube. The gas above the liquid in the left-hand limb of the U tube is alternately compressed and expanded by reason of the pressure pulses, and this produces oscillations in the mercury manometer *M*. The volume of the gas in the compression chamber *L* is fairly critical and can be adjusted when the apparatus is first set up by varying the amount of mercury in *L* until the best mixing of the liquid in the U tube is obtained. The movement of the mercury in *M* gives a visual indication of the rate and magnitude of the surging of the liquid which is being frozen. The main air stream passes to waste after traversing the trap *T*, immersed in liquid air, which has been inserted to reduce the vapour pressure of mercury in the effluent gas. The gas which pulsates to and fro immediately above the liquid in the right-hand limb of the U tube slowly interchanges with the gas in the line *F*. The liquid sample is protected from any impurities in this main air line by the column of silica gel *G*.

Efficient mixing in the U tube is produced by the stainless-steel helices of external diameter 3/8 in., made of wire of 1/16-in. diameter.

The U tube has square corners to allow the thermistor pocket to terminate at a point very near the bottom of the left hand limb. The position of the sensitive thermistor tip is important as visual inspection has shown that the last drops of liquid collect at this point at a time when the whole charge is nearly frozen. The thermistor is inserted in the pocket so that the sensitive tip is 1 mm. from the bottom of the inside of the pocket.

The design of the helices was conditioned by the following observations. Adequate mixing does not occur if the U tube is employed without helices, for the liquid then moves as a whole with merely local turbulence. On the other hand, restriction of free movement by too many baffles causes the liquid to become trapped in small pockets, and then the thermistor fails to record the temperature of the bulk liquid–solid mixture. The result of inadequate mixing is to produce a freezing curve of the wrong shape (see page 203 for a discussion on the shape of the curve).

The gas in the left-hand section of the U tube is in a closed system bounded by the mercury in the manometer *M* on one side and by the liquid in the freezing-point apparatus on the other, and therefore as the system cools the pressure of this gas falls. The average gas pressure in the other limb of the U tube however remains constant, because as the temperature falls more air is taken in from the line *F*. The pressures in the two sections can be equalised by manipulating the tap *J*, and this is done from time to time during the preliminary cooling.

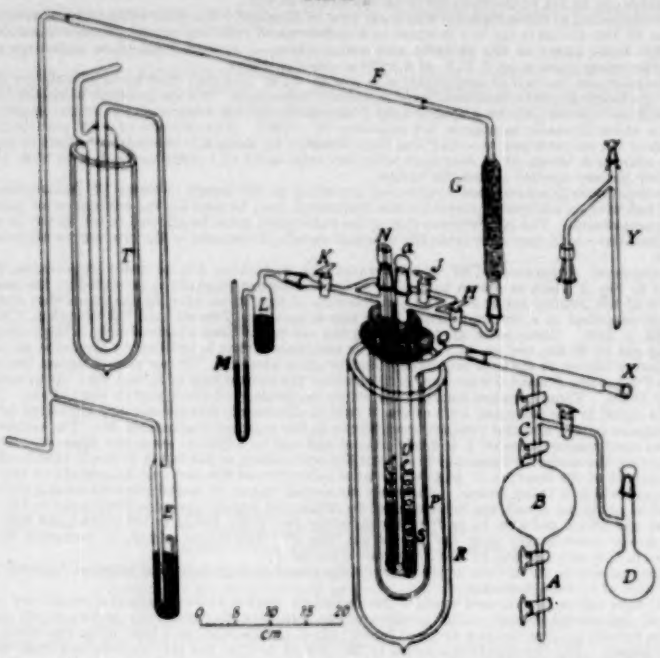
Cooling media suitable for different freezing temperatures have been suggested elsewhere (*e.g.*, Glasgow, Streiff, and Rossini, *loc. cit.*). The rate of cooling is adjusted by varying the gas pressure in the Dewar jacket *P* during the preliminary stages of cooling. The jacket is silvered except for two strips 0·5 × 8 cm. which are used as inspection windows. The jacket *P* can be evacuated by means of a mercury-vapour pump backed by a Metrovac oil pump with a trap immersed in liquid nitrogen inserted in the gas line to remove traces of mercury vapour (not shown in Fig. 2). The system of vessels, *A*, *B*, *C*, and *D* (Fig. 2) has proved to be useful for the introduction of controlled amounts of air to the vacuum jacket. The approximate volumes used were *A* = 0·6 c.c., *B* = 500 c.c., *C* = 1·2 c.c., and *D* = 150 c.c. Dry air at atmospheric pressure is admitted into *A*, and portions of this mass of gas can be expanded

into *B*, *C*, and *D*, and finally a selected volume of this gas at a low pressure can be admitted to the jacket *P*.

The U tube must be held symmetrically within the jacketted vessel *P*, and centring of the tube is ensured by the wooden platform *Q* which is held rigidly in position by a collar (see Fig. 2).

The method chosen to induce crystallisation in the slightly supercooled liquid depends upon circumstances. A convenient method, when it can be applied, is to employ the apparatus *Y* (Fig. 2) which can be connected to the U tube by interchange with the ground glass joint *a*. Two steel ball bearings, 3/32" in diameter, are cooled in the vertical tube of *Y* just before seeding is required. These balls can be moved up the tube by means of a permanent magnet and allowed to fall down the sloping

FIG. 2.



A, *B*, *C*, *D*. *Gas volumes for dosing.*
E. *Pulsing meter.*
F. *Gas line.*
G. *Silica gel.*
H, *J*, *K*. *Taps*, 4 *mm. bore.*
L. *Compression chamber.*
M. *Mercury manometer.*
N. *Cap carrying thermistor pocket.*
P. *Dewar flask with variable vacuum.*
Q. *Wooden platform supporting* U *tube.*
R. *Dewar flask containing cooling medium.*
S. *Stainless steel helices.*
T. *Trap in effluent gas line.*
U. U *tube containing liquid under examination* (46 *cm. in length, tube* 11 *mm. I.D.*).
X. *Joint to high vacuum line.*
a. *Glass cap* (*B.* 19) *which can be interchanged with sealing arrangement Y.*
Y. *Seeding apparatus containing ball bearings.*

tube into the right-hand side of the U tube when crystallisation is to be induced. This method does not always produce successful results with liquids which supercool readily or with liquids which freeze at a very low temperature, but where this technique can be employed contamination of the sample with moisture is avoided. An alternative method is to insert a cooled stainless-steel rod through *a* (Fig. 2) while the pulses are momentarily stopped, but even this simple procedure can yield erratic results with substances having more than one crystalline form (*e.g.*, α-picoline). In such circumstances an injector made by passing a thin stainless-steel rod down the centre of a close-fitting glass tube has proved useful because a plug of solid can be caused to crystallise in the tip of the ejector and can then be held until seeding is required at some temperature at which the desired crystalline form is stable. The solid can be ejected into the supercooled liquid by a thrust on the stainless-steel plunger.

The only heat liberated by the stirring in the present equipment is that produced by the friction of the liquid against the obstacles used to produce turbulence. Direct measurement on a typical example has shown that at 106 pulses per minute this heat is generated at approx. 7% of the rate at which heat is extracted in the cooling process.

Recording of the Freezing-point Curves.—10 C.c. of liquid samples may be used in the apparatus, although it is preferable to use double this amount. To carry out a determination the apparatus is assembled, the resistances in the arms of the Wheatstone bridge are adjusted to values suitable for the temperature at which freezing will occur, pressure in the two limbs of the U tube is equalised, and the pulses are started at a rate of 106 per minute. The Dewar vessel *R* (Fig. 2) containing the refrigerant is placed in position and, if a very wide temperature interval has to be covered before the freezing temperature is reached, dry air is admitted to the vacuum jacket *P* through a tap on the vacuum line (not shown) in order to accelerate the cooling. The jacket *P* is evacuated as soon as the temperature has fallen sufficiently, and doses of air at low pressure are admitted through the system *A*, *B*, *C*, *D*, until the desired cooling rate has been obtained. Rates are normally selected so that the total time of freezing is approx. 1½ hours. From time to time the levels of the liquid in the U tube are balanced by means of tap *J* (Fig. 2).

Crystallisation is induced by one of the methods described above. The liquid levels are balanced immediately following each attempt at seeding, but are not again adjusted once crystallisation has started. The temperature–time curve is then plotted on the recorder.

Treatment of Experimental Observations.

The theory of the use of freezing-point curves for determining impurities has frequently been discussed (see page 199 for references). The assumption that the main component crystallises first, leaving the impurity in the liquid is common to all these treatments.

White (*loc. cit.*) appears to have been the first to recognise that, if under these conditions the depression of the freezing point is proportional to the mol. fraction of impurity in the liquid, then the temperature difference between the initial freezing point and that when half the material is frozen is equal to the temperature depression originally produced by the impurity. The molar percentage of impurity and the true freezing point of the pure material can thus be found.

Rossini *et al.* (*loc. cit.*) have discussed a thermodynamically more exact approach which involves higher approximations, but for many purposes the simpler treatment appears to be sufficient, particularly since, as Schwab and Wichers (*loc. cit.*) point out, the rate of cooling is rarely, if ever, exactly constant. Schwab and Wichers therefore suggest that the amount of impurity be calculated by proportional parts from a freezing-point curve of the original material and from another curve for the same material obtained after a known amount of impurity has been added. Both curves should be measured under the same conditions.

In view of the uncertainties inherent in the technique we have used the simple method of calculation employed by Stull (*i.e.*, essentially White's method) when the cryoscopic constant has already been reported and when a high accuracy is not required. If a higher accuracy is needed or if the cryoscopic constant is not known, Schwab and Wicher's method of proportional parts is used.

The efficacy of any equipment for determining freezing-point curves can be examined by analysing the shape of the curves. Subject to the usual assumptions it follows from the argument used by White that

$$[(1 - x)/x]\Delta t = t^\circ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where Δt is the difference between the temperature at the initial freezing point at time z_0 and that at time z, x is the fraction frozen at time z, and t° is the depression of the freezing point of the pure component produced by the impurity originally present.

If the cooling rate is constant, then approximately

$$x = (z - z_0)/(z_t - z_0) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where z_0 is the time when freezing starts, z_t is the time when all the liquid has frozen, and z is the time when a fraction x is frozen.

The form of these equations shows that, on the temperature–time plot, Δt should increase as x increases, and that the rate of increase of Δt with time should itself increase with z. Fig. 1, curves 2 and 3, shows that smooth curves are obtained with the present apparatus and that they are qualitatively of the correct shape.

If equations (1) and (2) are obeyed, then $[(1 - x)/x]\Delta t$ and $[(z_t - z)/(z - z_0)]\Delta t$ should be constant. The table contains the more detailed analysis of some experimental results obtained with 20-c.c. samples for which x has been calculated from equation (2) and Δt is expressed in arbitrary units equal to the deflection of the galvanometer in divisions. These units have different values in terms of temperature for the two samples.

Values of $[(1 - x)/x]\Delta t$. *Total time of curves* = 86 *mins.*

	$[(1 - x)/x]\Delta t$.			$[(1 - x)/x]\Delta t$.	
x, calc. from equation (2).	Benzene, 99·73 mols.-% pure.	2 : 6-Lutidine, 99·1 mols.-% pure.	x, calc. from equation (2).	Benzene, 99·73 mols.-% pure.	2 : 6-Lutidine, 99·1 mols.-% pure.
0·1	13·5	23	0·6	12·6	28
0·2	10·0	24	0·7	12·4	24
0·3	10·5	28	0·8	12·0	19
0·4	12·0	30	0·9	9·0	11
0·5	13·0	31			

The table indicates that the curves obey equations (1) and (2) up to $x = 0{\cdot}70$, and therefore equilibrium between solid and liquid would appear to be maintained until 70% of the charge is frozen.

The freezing-point results for 184 hydrocarbons obtained by the reciprocating-stirrer method recorded in the " Supplement to National Bureau of Standards Circular 398 " (January 1st, 1949) have been analysed by us to provide a standard of accuracy against which to compare the performance of our apparatus. The results in the Circular are expressed as mol.-% of impurity $\pm$ a certain percentage. The parameter most directly measurable by the freezing-point method is the impurity, so that it is natural to express the uncertainty of the results as a fraction of the impurity. The mean value of the ratio $\pm$ percentage/mol. percentage for the 184 hydrocarbons listed is 0·54, *i.e.*, the value designated as $\pm$ is usually approximately one-half of the impurity determined. Thus a sample would be described as 99·6 $\pm$ 0·2 mols.-% pure.

A sample of benzene which was found to be 99·90 mols.-% pure in the present apparatus, with the method of calculation employed by Stull and a cryoscopic constant of 5·12° per 1000 g. of benzene gave a value of 99·77 mols.-% pure by the proportional-parts method. To the same sample of benzene was added in succession 0·048 and 0·144 mol.-% of impurity, *i.e.*, impurity in the ratio 1 : 3, and the depressions of temperature when the samples were half frozen were as 1 : 3·5.

The apparatus described thus appears to yield results at least as accurate as the methods in common use.

Our thanks are due to Mr. A. J. Cook for assistance with the experimental work and to Mr. C. G. Andrews for carrying out the construction of numerous models in glass which were used in the development of the design discussed here. The work described above has been carried out as part of the research programme of the Chemical Research Laboratory and this paper is published by permission of the Director of the Laboratory.

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47. *The Preparation of the Mononitrobenzaldehydes.*

By W. Davey and J. R. Gwilt.

o- and *p*-Nitrobenzaldehydes have been prepared by the oxidation of the corresponding nitrocinnamic acids. Nitration of benzylidene diacetate in acetic acid or anhydride solution with copper nitrate yields *p*-nitrobenzylidene diacetate, whilst nitration of the diacetate in acetic anhydride solution with nitric acid gives *o*-nitrobenzylidene diacetate. Nitration of acetophenone in acetic acid solution with copper nitrate yields *p*-nitrobenzylidene diacetate, and the mechanism of this reaction has been elucidated. Other metal nitrates are less effective than copper nitrate as nitrating agents for benzylidene diacetate. Hydrolysis of nitrobenzylidene diacetates is satisfactorily achieved by the use of suspensions of magnesium hydroxide.

Mononitrobenzaldehydes were required for the preparation of substituted benzaldehydes and of substituted chalcones; *m*-nitrobenzaldehyde is readily prepared by the direct nitration of benzaldehyde but the preparation of the *o*- and *p*-isomers presents some difficulties. Although some *o*-nitrobenzaldehyde is produced in the direct nitration of benzaldehyde (Friedländer, *Ber.*, 1881, **14**, 2803) it cannot easily be isolated from the reaction product. The preparation of *o*- and *p*-nitrobenzaldehydes has been investigated by three methods: (*a*) oxidation of the nitrotoluenes by the chromic acid–acetic acid–anhydride method, (*b*) oxidation of the nitrocinnamic acids, and (*c*) nitration of benzaldehyde and of its diacetate.

Oxidation of nitrotoluenes by the methods of *Org. Synth.*, Coll. Vol. II, p. 441, and Vol. **24**,

p. 75, gave the required products, but from *o*-nitrotoluene large amounts of tar were always obtained and the yield of aldehyde was low. In view of this and of the considerable risk of explosion attendant on the use of chromic acid in acetic anhydride (Tuey, *Chem. and Ind.*, 1948, 766), alternative methods of preparation were investigated.

Acetyl or benzoyl nitrate has been used for selective *ortho*-nitration of organic compounds but their use is limited by the risk of explosion (Pictet and Khotinsky, *Ber.*, 1907, **40**, 1163). Menke (*Rec. Trav. chim.*, 1925, **44**, 141, 269) has shown that acetic anhydride and copper, nickel, iron, or cobalt nitrate effect *ortho*-nitration in the same way as acetyl nitrate, but without the danger of explosion. Bacharach (*J. Amer. Chem. Soc.*, 1927, **49**, 1522) has confirmed this and shown that lithium nitrate yields mainly *p*-nitro-compounds. Nitration of cinnamic acid in acetic anhydride solution by means of hydrated copper nitrate failed to give *o*- and *p*-nitrocinnamic acids, which were therefore prepared by nitration of cinnamic acid or of its ethyl ester in nitric acid alone, or preferably in sulphuric acid, the acids being separated by utilising the low solubility of ethyl *p*-nitrocinnamate in ethanol (Drewson, *Annalen*, 1882, **212**, 150). Nitration of benzylidene diacetate, prepared from benzaldehyde by the method of Wegschneider and Späth (*Monatsh.*, 1909, **30**, 840), in acetic anhydride solution by means of hydrated copper nitrate yielded *p*-nitrobenzylidene diacetate in 52% yield, but the reaction was difficult to control an dnitration was therefore effected (in 79% yield), using acetic acid as solvent. Careful purification of benzaldehyde was essential for maximum yields, even redistilled samples of the aldehyde reacted violently with acetic anhydride with excessive evolution of heat. Attempts to moderate the reaction between impure benzaldehyde and acetic anhydride by the addition of acetic acid were not successful and led to incomplete formation of diacetate. Nitration of benzylidene diacetate, formed *in situ*, from pure benzaldehyde has also been achieved by this method. Commercial samples of benzaldehyde have been nitrated in acetic acid solution with copper nitrate to give *p*-nitrobenzylidene diacetate in 12% yield, although it has not proved possible to prepare benzylidene diacetate from benzaldehyde and acetic acid by a method analogous to that using acetic anhydride (cf. Wegschneider and Späth, *loc. cit.*). Other metal nitrates were found to be less useful than copper nitrate in these reactions, lead nitrate failing to react and sodium nitrate causing deflagration.

Baker and Ingold (*J.*, 1930, 431) showed that the nitration of benzaldehyde with acetic anhydride and nitric acid gave 62·6% of *o*–*p*- and 37·4% of *m*-nitration, the reaction proceeding *via* the diacetate (*p*-nitrobenzylidene diacetate was isolated from the reaction mixture). The change in position of nitration with different experimental conditions has been summarised by Baker and Moffitt (*J.*, 1931, 316). Nitration of benzylidene diacetate, formed *in situ*, in acetic anhydride solution with nitric acid was vigorous and led to *o*-nitrobenzylidene diacetate (43%) and *p*-nitrobenzoic acid (26%), whilst nitration at low temperatures gave *o*-nitrobenzaldehyde in 41% yield. A mixture of nitric and sulphuric acids, at low temperatures, gave *o*- and *m*-nitrobenzaldehyde in 33% and 43% yield, respectively. Excess of sulphuric acid led to the hydrolysis of the diacetate and formation of *m*-nitrobenzaldehyde as the main product. This *ortho*-nitrating effect of nitric acid–acetic anhydride has previously been reported by Witt and Uterman (*Ber.*, 1906, **39**, 3903) and the preparation of *o*-nitrocinnamic aldehyde in 36% yield by Mills and Evans (*J.*, 1920, 1037) is a further example for *o*-nitro-aldehydes. Nitric acid, in contrast to copper nitrate, fails to nitrate benzylidene diacetate in acetic acid solution.

Ketones do not form diacetates, but acetophenone undergoes oxidation and nitration to *p*-nitrobenzylidene diacetate in 40% yield when treated with acetic acid and copper nitrate. The mechanism of this reaction has been found to involve oxidation of the acetophenone to benzoylformic acid, loss of carbon dioxide to give benzaldehyde, formation of benzylidene diacetate, and nitration. Benzoylformic acid yields benzylidene diacetate on heating with acetic anhydride, and *p*-nitrobenzylidene diacetate on nitration with acetic anhydride or acetic acid and copper nitrate.

The results of these nitrations are summarised in the table.

Some difficulty was encountered in the hydrolysis of *p*-nitrobenzylidene diacetate by the method of *Org. Synth.*, Coll. Vol. II, p. 441. It has been found possible to hydrolyse nitrobenzylidene diacetates in high yields by means of magnesium hydroxide suspensions. Alkaline hydrolysis of aldehyde diacetates is not normally feasible as the high concentration of alkali which must be present initially to ensure complete hydrolysis leads to condensation of the aldehyde formed in the early stages of the hydrolysis. It has been found that if the hydrolysis of nitrobenzylidene diacetates is carried out at 100° with increasing concentrations of sodium hydroxide, the Cannizzaro reaction becomes appreciable when the alkali concentration reaches about 0·01N. (pH about 12 at 24°). Condensation could be avoided by adding the alkali at

such a rate that the critical pH is never reached and this can be conveniently achieved by hydrolysing these diacetates with magnesium hydroxide suspensions, since the pH of its pure aqueous suspension is about 10·4 (at 24°).

Nitration of cinnamic acid, ethyl cinnamate, benzylidene diacetate and acetophenone.

Reactants.		Conditions.	Products.
1. Cinnamic acid :	HNO_3	3 hrs., <10°	49% *o*- + 39% *p*-nitrocinnamic acid
2. "	HNO_3–H_2SO_4	4 hrs., <20°	50% *o*- + 39% *p*-nitrocinnamic acid
3. "	HNO_3–AcOH	4 hrs., <20°	Unchanged
4. Ethyl cinnamate :	HNO_3	4 hrs., <20°	56% *o*- + 27% *p*-nitrocinnamic acid
5. "	HNO_3–H_2SO_4	4 hrs., <20°	43% *o*- + 42% *p*-nitrocinnamic acid
6. Cinnamic acid :	Ac_2O–$Cu(NO_3)_2$	Uncontrolled	68% *o*- + 15% *p*-nitrobenzoic acid
7. Benzylidene diacetate :	Ac_2O–$Cu(NO_3)_2$	"	52% *p*-nitrobenzylidene diacetate
8. "	" AcOH–$Cu(NO_3)_2$	5 hrs., reflux	79% " "
9. Benzaldehyde :	AcOH–$Cu(NO_3)_2$	"	79% " "
10. Benzylidene diacetate :	Ac_2O–HNO_3 ...	118°	43% *o*-nitrobenzaldehyde + 26% *p*-nitrobenzoic acid
11. "	" " ...	4 hrs., <20°	41% *o*-nitrobenzaldehyde
12. "	" AcOH–HNO_3 ...	Uncontrolled	96% benzoic acid
13. "	" HNO_3–H_2SO_4 ...	3 hrs., <15°	33% *o*- + 43% *m*-nitrobenzaldehyde
14. Benzaldehyde :	HNO_3–H_2SO_4	4 hrs., <15°	80% *m*- + little *o*-nitrobenzaldehyde
15. Acetophenone :	AcOH–$Cu(NO_3)_2$	5 hrs., reflux	42% *p*-nitrobenzylidene diacetate

Experimental.

(All m p s are uncorrected.)

1. *Nitration of Cinnamic Acid with Nitric Acid Alone.*—Finely powdered cinnamic acid (30 g.) was added during 1 hour to vigorously stirred nitric acid (150 ml.; *d* 1·52) and the mixture stirred for a further 2 hours, the temperature being maintained below 10° by external cooling. The resulting paste was stirred into water (2·5 l.) and filtered, and the product washed free from mineral acid with cold water.

The air-dried product (38 g.) was suspended in ethanol (400 ml.), sulphuric acid (15 ml.; *d* 1·84) added, and the whole refluxed until dissolution was complete. The resulting solution was cooled to 0° and kept overnight in the refrigerator. The ethyl *p*-nitrocinnamate which had separated was filtered off and washed with cold ethanol (50 ml.), the filtrate and washings being combined. The ester, after recrystallisation from ethanol, was boiled with ethanol (200 ml.) and sulphuric acid [50 ml. (*d* 1·84) + 350 ml. of water] for 8 hours. After addition of water (500 ml.) the precipitated acid was filtered off, and purified by dissolution in sodium carbonate solution, filtration, and reprecipitation by hydrochloric acid. Recrystallisation of the product from ethanol gave *p*-nitrocinnamic acid (15·2 g., 39%), m. p. 286° (Müller, *Annalen*, 1882, **212**, 126, gives m. p. 286°).

Hydrolysis of the filtrate was achieved by the addition of water (500 ml.) and refluxing for 12 hours. The *o*-nitrocinnamic acid was precipitated by pouring the mixture into water and purified as in the case of the *p*-nitro-acid, to give an acid (19·2 g., 49%), m. p. 240° (Müller, *loc. cit.*, gives m. p. 240°).

2. *Nitration of Cinnamic Acid with Nitric and Sulphuric Acids.*—Cinnamic acid (30 g.), dissolved in sulphuric acid (200 ml.; *d* 1·84) was nitrated by the addition of nitric acid (11 ml.; *d* 1·52) during an hour, and stirring for a further 3 hours, the temperature being kept below 20°. Isolation of the mixed acids by precipitation with water, filtration, and washing gave a product which was separated as before to give *p*- (19·5 g., 39%; m. p. 286°) and *o*-nitrocinnamic acid (19·5 g., 50%; m. p. 240°).

3. *Nitration of Cinnamic Acid with Acetic and Nitric Acids.*—Addition of nitric acid [11 ml. (*d* 1·52) or 50 ml. [*d* 1·52)] to cinnamic acid (30 g.) in glacial acetic acid (250 ml.) afforded only unchanged cinnamic acid.

4. *Nitration of Ethyl Cinnamate with Nitric Acid Alone.*—Ethyl cinnamate (50 g.) was nitrated by adding it slowly to cooled nitric acid (250 ml.; *d* 1·52) and stirring for a further 3 hours, at <20°. The mixed nitro-esters were isolated by pouring the mixture into water (2·5 l.), filtration, and washing. Separation was achieved by dissolving the mixture in ethanol (500 ml.), cooling to 0°, and allowing the *p*-ester to separate overnight in the refrigerator. Hydrolysis by the methods already described and purification of the acids gave *p*- (15 g., 27%; m. p. 286°) and *o*-nitrocinnamic acid (31 g., 56%; m. p. 240°).

5. *Nitration of Ethyl Cinnamate with Sulphuric and Nitric Acids.*—Nitration of ethyl cinnamate (50 g.) dissolved in sulphuric acid (150 ml.; *d* 1·84) as in (2) above, using nitric acid (20 ml.; *d* 1·52), gave *p*- (23 g., 42%; m. p. 286°) and *o*-nitrocinnamic acid (24 g., 43%; m. p. 240°).

6. *Nitration of Cinnamic Acid with Acetic Anhydride and Copper Nitrate.*—Nitration in acetic anhydride with hydrated copper nitrate, warming to 65—70°, and allowing the reaction to proceed spontaneously afforded only *o*- and *p*-nitrobenzoic acids. Under these experimental conditions *o*- and *p*-nitrocinnamic acids are oxidised to the corresponding nitrobenzoic acids. At 20° unchanged cinnamic acid and only 10% of *o*- and *p*-nitrocinnamic acid were obtained.

Oxidation of nitrocinnamic acids to nitrobenzaldehydes. *o*-Nitrocinnamic acid (10 g.) was dissolved in a solution of sodium carbonate (6 g.) in water (750 ml.), benzene (200 ml.) added, and the mixture cooled to 10° by addition of ice and external cooling. Oxidation was achieved by the addition of potassium permanganate solution (250 ml.; 6%) with vigorous stirring to ensure thorough mixing, the temperature being kept below 10° by the addition of ice. Stirring was continued for a further hour, the product filtered, and the manganese dioxide washed with benzene (50 ml.). The benzene layer was separated

and the aqueous layer extracted with benzene (2 × 50 ml.) which was added to the main extract. After being washed with water, the benzene extract was dried, and the benzene distilled off. The residue was dissolved in toluene (10 ml.), light petroleum (70 ml.; b. p. 40—60°) added, and the solution cooled to 0°, to give *o*-nitrobenzaldehyde (5 g., 64%), m. p. and mixed m. p. 43° (oxime, m. p. 103°; acetone condensed with it in presence of sodium hydroxide to give indigo, soluble in chloroform). Extraction of the acidified aqueous layer with ether and removal of the ether gave *o*-nitrobenzoic acid, (1·7 g., 20%), m. p. and mixed m. p. 146°.

Oxidation of *p*-nitrocinnamic acid under identical conditions gave *p*-nitrobenzaldehyde (5·8 g., 74%), m. p. and mixed m. p. 106° (oxime, m. p. 132°), and *p*-nitrobenzoic acid (1·3 g., 15%), m. p. and mixed m. p. 237°.

7. *Nitration of Benzylidene Diacetate with Acetic Anhydride and Copper Nitrate.*—Benzaldehyde (12 g.) and acetic anhydride (60 g.) were stirred together, and 5 drops of sulphuric acid (*d* 1·84) added to catalyse the formation of the diacetate. After a further 15 minutes' stirring to complete the reaction, hydrated copper nitrate (30 g.) was added, the mixture warmed to 65°, and the vigorous reaction allowed to proceed spontaneously (see note below). When the temperature had fallen to 30°, water (500 ml.) and sulphuric acid [25 ml. (*d* 1·84) + 4 parts water] were added and the mixture set aside overnight. The precipitated *p*-nitrobenzylidene diacetate was filtered off, washed free from acid with water, and recrystallised from aqueous ethanol to give *p*-nitrobenzylidene diacetate (15 g., 52%), m. p. and mixed m. p. 122°. Hydrolysis of the diacetate is described later. Note: addition of copper nitrate to acetic anhydride may lead to an exothermic reaction.

Attempts to nitrate benzylidene diacetate in acetic anhydride solution with hydrated copper nitrate at <20° during 7 hours yielded only unchanged diacetate. Benzaldehyde is not nitrated by copper nitrate in acetic acid at <20°.

8. *Nitration of Benzylidene Diacetate with Acetic Acid and Copper Nitrate.*—Benzaldehyde (106 g.) was converted by acetic anhydride (250 ml.) and sulphuric acid (5 ml.; *d* 1·84) into the diacetate, which was isolated by precipitation with water. The separated diacetate was drained at the pump, dissolved in acetic acid (1 l.), and nitrated by refluxing it for 5 hours with hydrated copper nitrate (300 g.). The product was isolated as before, and the *p*-nitrobenzylidene diacetate (200 g., 79%) was hydrolysed by the method of *Org. Synth.*, Coll. Vol. II, p. 441, to give *p*-nitrobenzaldehyde (110 g., 73% based on the benzaldehyde taken), m. p. and mixed m. p. 106° (phenylhydrazone m. p. 156°; oxidation with alkaline permanganate gave *p*-nitrobenzoic acid, m. p. and mixed m. p. 237°).

Nitration has also been effected to give similar yields of diacetate and aldehyde by adding the acetic acid and copper nitrate to the acetic anhydride solution of the aldehyde without isolating the diacetate, and this is the most satisfactory method.

9. *Nitration of Benzaldehyde with Acetic Acid and Copper Nitrate, without Intermediate Diacetate Formation.*—Benzaldehyde (25 g.) was refluxed with glacial acetic acid (200 ml.) and hydrated copper nitrate (60 g.) for 5 hours, and the product poured into water, made alkaline with aqueous ammonia and then just acid to litmus with dilute sulphuric acid. The precipitate, on recrystallisation from aqueous ethanol, gave *p*-nitrobenzylidene diacetate (7 g., 12%), m. p. and mixed m. p. 122°.

Reaction between Benzaldehyde and Acetic Acid.—Benzaldehyde (12 g.), glacial acetic acid (60 g.), and sulphuric acid (0·5 ml.; *d* 1·84) were stirred together for periods up to 3 hours at room temperature or up to 30 minutes at the b. p. of the mixture. In no case was benzylidene diacetate obtained on dilution with water, benzaldehyde separating in all cases; there was no evidence of appreciable reaction from time–temperature measurements, typical results being:—

	Temperature.	
Time, min.	Mixture as above.	Acetic acid replaced w./w. by acetic anhydride.
0	18°	18°
0·25	20	50
15	19·5	35

The use of mixtures of acetic acid and anhydride led in all cases to incomplete formation of benzylidene diacetate.

Use of Other Metal Nitrates.—Nitrations of benzylidene diacetate (21 g.) in acetic acid (100 ml.) using various metal nitrates under the conditions previously described were carried out with the following results:

Metal nitrate and wt. (g.) used.		Yield of *p*-nitrobenzylidene diacetate. Wt. (g.).	%	Metal nitrate and wt. (g.) used.		Yield of *p*-nitrobenzylidene diacetate. Wt. (g.).	%
Zinc,	30	6·0	23	Cobalt,	35	1	4
Ferric,	40	5·0	19	Calcium,	25	0	0
Bismuth,	50	5·0	19	Lead,	50	0	0
Nickel,	35	3·0	12	Sodium,	25	deflagration	
Magnesium,	30	2·0	8				

10. *Nitration of Benzylidene Diacetate with Acetic Anhydride and Nitric Acid.*—Benzaldehyde (120 g.) was added to acetic anhydride (500 ml.), and sulphuric acid (10 ml.; *d* 1·84) added slowly with vigorous stirring. The solution was stirred for a further 30 minutes and nitric acid (200 ml.; *d* 1·42) added at the rate of 25 drops per minute, the vigorous reaction maintaining the temperature at 118°. More nitric acid (50 ml.) was then added more rapidly, and the mixture then allowed to cool and poured into a large excess of water. The separated material was filtered off, washed with cold water, and refluxed with ethanol (400 ml.), water (400 ml.), and sulphuric acid (40 ml.; *d* 1·84) for 1 hour. The product was then rapidly steam-distilled to leave a residue of *p*-nitrobenzoic acid (40 g., 26%), m. p. and mixed m. p. 237° (*p*-nitrobenzyl ester m. p. 167°). Extraction of the distillate with ether and removal of the ether gave

a residue which after crystallisation from toluene and 4 volumes of light petroleum (b. p. 40—60°) gave *o*-nitrobenzaldehyde (74 g., 43%), m. p. 42—43° (oxidised by alkaline permanganate to *o*-nitrobenzoic acid, m. p. 147°; acetone condensed in presence of sodium hydroxide to give indigo, soluble in chloroform).

11. *Nitration of Benzylidene Diacetate with Acetic Anhydride and Nitric Acid at Low Temperatures.*—Benzaldehyde (12 g.), dissolved in acetic anhydride (100 ml.), was nitrated by the slow addition of nitric acid (30 ml.; *d* 1·52) with rapid stirring and external cooling, the temperature being kept at <20°. After a further 3 hours' stirring the nitration mixture was set aside at room temperature overnight. The product was poured into water (2 l.), and the separated solid filtered off, washed free from acid and crystallised from toluene–light petroleum, to give *o*-nitrobenzaldehyde (6 g., 41%), m. p. and mixed m. p. 42—43°. In this preparation hydrolysis of the diacetate occurred during isolation, and the above method represents the most convenient method of preparation of *o*-nitrobenzaldehyde by direct nitration of benzaldehyde.

12. *Nitration of Benzylidene Diacetate with Acetic and Nitric Acids.*—Attempts to nitrate benzylidene diacetate in acetic acid at elevated temperatures led to the formation of benzoic acid, whilst at <20° there was no nitration during 2 days.

13. *Nitration of Benzylidene Diacetate with Sulphuric and Nitric Acids.*—Nitration of benzylidene diacetate (21 g.), dissolved in sulphuric acid (100 ml.; *d* 1·84), with nitric acid (10 ml.; *d* 1·52) at <15° led to *o*- (5 g., 33 %) m. p. 42°, and *m*-nitrobenzaldehyde (6·5 g., 43%), m. p. and mixed m. p. 58°. Increase in the proportion of sulphuric acid or the use of mixed acid for the nitration led to the formation of *m*-nitrobenzaldehyde as the main product, hydrolysis of the diacetate occurring before nitration.

14. *Preparation of* m-*Nitrobenzaldehyde.*—Nitration of redistilled benzaldehyde (106 g.), dissolved in sulphuric acid (300 ml.; *d* 1·84), with mixed acid [70 ml. of nitric (*d* 1·52) + 150 ml. of sulphuric acid (*d* 1·84)] at <15° gave *m*-nitrobenzaldehyde (121 g., 80%), m. p. and mixed m. p. 58°. Small amounts (*ca.* 5 g.) of impure *o*-nitrobenzaldehyde were isolated from the acid liquors by ether-extraction, but the product was extremely difficult to purify.

15. *Nitration of Acetophenone with Acetic Acid and Copper Nitrate.*—Acetophenone (25 g.) was refluxed for 5 hours with acetic acid (250 ml.) and hydrated copper nitrate (60 g.), and the mixture poured into a large excess of water and set aside overnight. The product was made alkaline with aqueous ammonia and then just acid with dilute sulphuric acid, and the precipitate filtered off, washed with water, and recrystallised from aqueous ethanol to give *p*-nitrobenzylidene diacetate (22 g., 42%), m. p. and mixed m. p. 122°.

Reaction Mechanism.—Benzoylformic acid (5 g.) was refluxed with acetic anhydride or acid (50 ml.) and hydrated copper nitrate (10 g.). Pouring the mixture into water gave *p*-nitrobenzylidene diacetate (3·1 g.; 2·2 g.), m. p. and mixed m. p. (after crystallisation from ethanol) 122°.

Benzoylformic acid (5 g.) was refluxed for 2 hours with acetic anhydride (50 ml.) and one drop of sulphuric acid, or glacial acetic acid (50 ml.). Benzylidene diacetate (3 g.; m. p. and mixed m. p. 46°) and benzaldehyde (2·2 g., identified as 2 : 4-dinitrophenylhydrazone) respectively were obtained on pouring the mixtures into water.

Oxidation of o- *and* p-*Nitrotoluenes.*—Oxidation of *p*-nitrotoluene by the method of *Org. Synth.*, Coll. Vol. II, p. 441, gave *p*-nitrobenzylidene diacetate in 40% yield, whilst oxidation of *o*-nitrotoluene gave 20—25% yields of the *o*-nitro-diacetate and always led to the formation of much tar.

Hydrolysis of Diacetates.—Difficulty was encountered in the acid hydrolysis of *p*-nitrobenzylidene diacetate by the method of *Org. Synth.* but rapid and complete hydrolysis of diacetates was effected as follows. The diacetate (50 g.) was refluxed with a 2·5% suspension (800 ml.) of magnesium hydroxide for 2 hours. The product was cooled, the excess of magnesium hydroxide dissolved in dilute sulphuric acid (50—60 ml.; 5N.), and the mixture chilled in ice. The aldehyde which separated was filtered off and recrystallised. Additional small amounts of aldehyde could be recovered by ether-extraction of the mother-liquors. Yields of 90—95% have been obtained.

"Milk of magnesia," diluted with 2½ parts (vol.) of water, was most suitable, as the particles are very finely dispersed but the suspension is free from any added dispersing agent.

Thanks are due to Messrs Chas. H. Phillips Chemical Co. for gifts of "Milk of magnesia."

ACTON TECHNICAL COLLEGE, HIGH ST., W.3. [*Received, October 18th*, 1949.]

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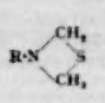
48. *The Action of Hydrogen Sulphide on Certain Methyleneimines. Part I.*

By ERIC R. BRAITHWAITE and JOHN GRAYMORE.

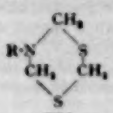
Hydrogen sulphide reacts with *N*-methylene*cyclo*hexylamine in the presence of formaldehyde to give N-cyclo*hexylthioformaldine*, but in the absence of formaldehyde the main product is 5-cyclo*hexyl*-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine*. With methylenebenzylamine, hydrogen sulphide and formaldehyde give a single product, 3 : 5-dibenzyltetrahydro-1-thia-3 : 5-diazine. This difference can be ascribed to the dimeric structure of methylenebenzylamine.

WOHL (*Ber.*, 1886, **19**, 2345) obtained a product from formaldehyde saturated with hydrogen sulphide by adding methylamine. He described it as methylthioformaldin (II; R = CH_3). Le Fèvre (*J.*, 1935, 865) obtained a four-membered ring compound formulated as (I; R = CH_3) by first saturating an aqueous solution of methylamine with hydrogen sulphide and then adding formaldehyde solution; the author observed that on dissolving his product in warm acetone,

conversion into Wohl's methylthioformaldin took place. No other six-membered ring compound of the type described by Wohl was obtained.



(I.)



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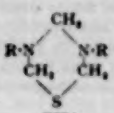
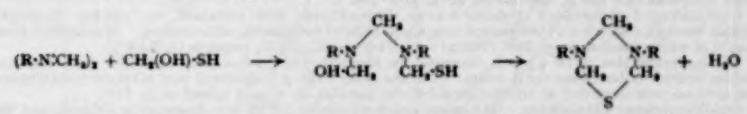


(III.)

We considered that it should be possible to obtain compounds of types (I), (II), and (III) from suitable amines, formaldehyde, and hydrogen sulphide. Formaldehyde is known to condense with *cyclo*hexylamine (*J.*, 1947, 1118) and with benzylamine to give readily crystallisable methyleneimines. As the formation of a thialdine in the Wohl–Le Fèvre reaction is probably preceded by the formation of a methyleneimine, it seemed reasonable to use the methyleneimines as starting points. Consequently, a study of the reaction was made with formaldehyde and hydrogen sulphide on the one hand, and *N*-methylene*cyclo*hexylamine or *N*-methylenebenzylamine on the other.

Aqueous-alcoholic solutions of the methyleneimines were accordingly treated with formaldehyde. The mixtures were cooled to keep the temperature below 25°, and a stream of hydrogen sulphide passed in. In each case a single crystalline product separated in excellent yield, but whereas *N*-methylene*cyclo*hexylamine gave a *thioformaldine* of type (I; R = C_6H_{11}), *N*-methylenebenzylamine gave **3 : 5-*dibenzyltetrahydro*-1-*thia*-3 : 5-*diazine*** (III; R = CH_2Ph).

It had been noted that, although both methyleneimines can be precipitated from alcoholic solution by the addition of water, yet *N*-methylene*cyclo*hexylamine was not precipitated from alcoholic solution even by the addition of excess of formaldehyde (40% formalin). *N*-Methylenebenzylamine on the other hand was precipitated. These observations seemed to indicate that the former, a monomer, adds formaldehyde to give in all probability $C_6H_{11}N(CH_2{\cdot}OH)_2$, which condenses with hydrogen sulphide to give (I; R = C_6H_{11}). *N*-Methylenebenzylamine, a dimer, could not combine with formaldehyde and it is therefore probable that the dibenzyl compound (III; R = CH_2Ph) is produced as follows:



An aqueous-alcoholic solution of *N*-methylene*cyclo*hexylamine in the absence of formaldehyde reacted exothermally with hydrogen sulphide. With the temperature kept below 25°, two crystalline compounds were eventually obtained, namely, **5-cyclo*hexyl*-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine*** similar to the thioformaldine described by Wohl (II; R = C_6H_{11}) and a smaller quantity of type (I).

Repeated attempts to make **5-*cyclo*hexyl-5 : 6-dihydro-1 : 3-dithia-5-azine** from (I) by the action of hydrogen sulphide in the presence of formaldehyde were unavailing, so it might well be that (I) and (II) (R = C_6H_{11}) are formed independently from the methyleneimine by condensation with $CH_2(OH){\cdot}SH$ and $CH_2(OH){\cdot}S{\cdot}CH_2{\cdot}SH$, respectively. The first stage in the reaction of hydrogen sulphide with the methyleneimine is undoubtedly the partial breakdown of the latter to give *cyclo*hexylamine,

$$C_6H_{11}{\cdot}N{:}CH_2 + H_2O + H_2S \longrightarrow C_6H_{11}{\cdot}NH_2 + CH_2(OH){\cdot}SH$$

since cyclo***hexylamine thiosulphate*** slowly separates from the residual liquor.

When hydrogen sulphide was passed into the aqueous-alcoholic solution of *N*-methylene-*cyclo*hexylamine without temperature control, the temperature rose rapidly with the separation of a voluminous non-nitrogenous solid. Its melting point and general properties indicated that it was the compound which Wohl obtained by the action of hydrogen sulphide upon an aqueous or alcoholic solution of hexamine. Wohl assigned to it the formula $(CH_2S)_n$. Analyses of the compound now obtained did not agree with his findings. It is hoped to deal with this problem later.

After removal of the bulky insoluble precipitate, the filtrate was allowed to evaporate spontaneously, leaving a residue of *cyclo*hexylamine thiosulphate. Marrin, Achterhof, Conway, and Boord (*J. Amer. Chem. Soc.*, 1931, **53**, 2682) showed that the hydrosulphides of certain

amines oxidised in air to the corresponding thiosulphates. The thiosulphates of *cyclo*hexylamine and *benzylamine* separated in considerable yields when air was blown through an alcoholic solution of the amine saturated with hydrogen sulphide.

All three thioformaldines decompose when heated with hydrochloric acid—(I) rapidly, (II) and (III) slowly—to give trithioformaldehyde (cf. Le Fèvre, *J.*, 1935, 865). Similarly, they all decompose when heated under reflux in alcoholic solution in a stream of hydrogen sulphide to give the non-nitrogenous compound described above.

Experimental.

*cyclo*Hexylthioformaldine (3-*cyclo*Hexyl-1-*thia*-3-*azetidine*).—*N*-Methylene*cyclo*hexylamine (5·0 g.), freshly prepared and recrystallised from ethanol, was dissolved in alcohol (50 c.c.), and formaldehyde (25 c.c. of a 40% solution) added. After a few minutes, hydrogen sulphide was passed in for 10 minutes, the temperature being kept below 25°. The resulting solid was removed. The process was repeated until no further yield (total, 4·3 g.) was obtained. The *thioformaldine* crystallised from acetone in needles, m. p. 118—120° (Found: C, 60·6; H, 9·4; N, 8·9. $C_4H_{11}NS$ requires C, 61·1; H, 9·5; N, 8·9%). It was soluble in acetone, methanol, benzene, chloroform, or light petroleum. A solution in ethanol gave with an alcoholic solution of hydrogen chloride a crystalline *hydrochloride*, m. p. >120° (decomp.) (Found: N, 7·17; Cl, 18·0. $C_4H_{12}NCIS$ requires N, 7·2; Cl, 18·3%).

The mother compound (0·4 g.) was dissolved in aqueous alcohol and heated under reflux (10 minutes). The solution was cooled, and water added, whereupon glistening needles were obtained which on recrystallisation gave 5-*cyclo*hexyl-5 : 6-dihydro-1 : 3-dithia-5-azine, m. p. and mixed m. p. 58°.

*cyclo*Hexylthioformaldine (1 g.), dissolved in dilute hydrochloric acid (50 c.c.) and heated under reflux, rapidly decomposed with evolution of formaldehyde and separation of trithioformaldehyde in needles (m. p. and mixed m. p. 216°). The mother-liquor after cooling and removal of the solid gave, with benzoyl chloride and sodium hydroxide, benzo*cyclo*hexylamide (m. p. and mixed m. p. with an authentic specimen 160°).

5-*cyclo*Hexyl-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine*.—Methylene*cyclo*hexylamine (26 g.) was dissolved in ethanol (50 c.c.), and water was added until the mixture remained faintly opaque. Hydrogen sulphide was passed in at 0° for 1—2 hours. The precipitate (5·8 g.) which separated was recrystallised first from aqueous alcohol and finally from ethanol, forming long needles, m. p. 58°, of the *dithia-azine* (Found: C, 53·35; H, 8·5; N, 7·1; S, 31·0. $C_5H_{11}NS_2$ requires C, 53·2; H, 8·4; N, 6·9; S, 31·5%). It was insoluble in water, moderately soluble in acetone, and soluble in benzene or chloroform.

The filtrate from the first precipitate slowly deposited needles, m. p. 105—106° (1 g.); these recrystallised from acetone in needles and were identified as *cyclo*hexylthioformaldine (m. p. and mixed m. p. 118°). The filtrate from the above was distilled into 2*N*-hydrochloric acid and gave *cyclo*hexylamine hydrochloride (m. p. and mixed m. p. 204—205°).

5-*cyclo*Hexyl-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine* *hydrochloride* was obtained by passing hydrogen chloride through a solution of the parent compound in light petroleum, with cooling. It separated from ethanol in white needles, m. p. 183° (Found: Cl, 14·9. $C_5H_{12}NCIS_2$ requires Cl, 14·6%).

The hydrochloride (0·75 g.) was dissolved in concentrated hydrochloric acid (10 c.c.), and the solution heated under reflux for 3 hours. A white solid (0·28 g.) separated and after recrystallisation from acetone was identified as trithioformaldehyde, needles, m. p. and mixed m. p. 216°.

*cyclo*Hexylamine Thiosulphate.—Methylene*cyclo*hexylamine (18 g.) was dissolved in ethanol, and the solution saturated with hydrogen sulphide for 5 hours, the temperature rising to 45°. The solid deposited was repeatedly washed with hot ethanol until no further solution appeared to take place. The solution was filtered hot, and, on cooling, silvery white plates of *cyclo*hexylamine thiosulphate separated, m. p. 198° (decomp.). It gave the usual reactions of thiosulphates (Found: C, 45·9; H, 8·4; N, 8·9. $C_{12}H_{32}O_3N_2S_4$ requires C, 46·15; H, 8·9; N, 8·9%). The insoluble residue, m. p. 175°, was nitrogen-free but its structure has not yet been determined. The thiosulphate was obtained directly by saturating an ethanolic solution of *cyclo*hexylamine with hydrogen sulphide and passing air through the mixture until no further precipitate was obtained. Recrystallised from ethanol it gave white leaflets, m. p. 198° (decomp.) [Found: 0·9995 g. ≡ 31·9 c.c. of 0·01*N*-iodine solution. $(C_6H_{11}\cdot NH_2)_2S_2O_3$ requires 31·8 c.c.].

3 : 5-*Dibenzyltetrahydro*-1-*thia*-3 : 5-*diazine*.—Methylenebenzylamine (5·0 g.) was dissolved in ethanol (50 c.c.), and formaldehyde (15 c.c. of a 40% solution) which had previously been saturated with hydrogen sulphide was added. A stream of hydrogen sulphide was passed in until the temperature rose to 25°. The solution became opaque after 15 minutes; it was set aside for 24 hours, and the crystals which separated were removed by filtration, and then recrystallised from ethanol in long needles, m. p. 92° (Found: C, 71·8; H, 7·05; N, 9·4, 9·5; S, 10·8. $C_{17}H_{20}N_2S$ requires C, 71·8; H, 7·0; N, 9·8; S, 11·0%). This 3 : 5-*dibenzyltetrahydro*-1-*thia*-3 : 5-*diazine* was dissolved in light petroleum, and the solution saturated with hydrogen chloride. The white *dihydrochloride* which separated was removed and crystallised from ethanol; it had m. p. 130—140° (decomp.) (Found: Cl, 20·1. $C_{17}H_{22}N_2Cl_2S$ requires Cl, 19·9%). When heated under reflux for 3 hours with concentrated hydrochloric acid, the parent substance (0·75 g.) gave trithioformaldehyde (0·1 g.).

Benzylamine Thiosulphate.—Benzylamine (10 g.) was dissolved in ethanol (40 c.c.), and the solution saturated with hydrogen sulphide. Air was passed through the mixture and *benzylamine thiosulphate* slowly separated in silvery leaflets (10 g.). These crystallised from ethanol in leaflets, m. p. 182° (decomp.) [Found: 0·9995 g. ≡ 30·2 c.c. of 0·01*N*-iodine. $(C_6H_5\cdot CH_2\cdot NH_2)_2S_2O_3$ requires 30·3 c.c.].

Analyses were by Drs. Weiler and Strauss.

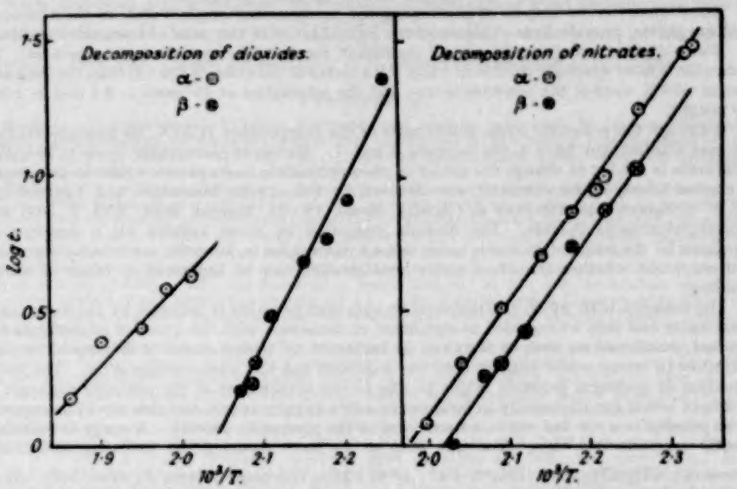
Plymouth and Devonport Technical College, Plymouth. [*Received, October 12th*, 1949.]

49. *Geometrical Isomerism of the Dioxides of Diphenylpiperazine.*

By G. M. Bennett and (Mrs.) Erika Glynn.

Diphenylpiperazine is oxidised by hydrogen peroxide to two isomeric di-*N*-oxides. The α-isomeride crystallises as an efflorescent octahydrate and a stable dihydrate which loses its water in a vacuum. The β-isomeride, formed in a proportion of about 1 in 10, is much the more soluble in water. It is isolated in the form $B,H_2O_2,2H_2O$, stable in a vacuum. The salts of these dioxides are usually anhydrous, free from hydrogen peroxide, and of the composition B,2HX. The isomeric hydrochlorides, nitrates, and picrates have been characterised and also the oxalate, sulphate, perchlorate, ferrocyanide, platinichloride and aurichloride of the α-dioxide. All these substances explode when heated, and the times required for explosion at various temperatures have been studied. The stability of its complex with hydrogen peroxide indicates that the β-isomeride has the *cis*-configuration.

Di-*N*-oxides of suitable diamines should exist in diastereoisomeric or *cis-trans*-forms analogous to those of the dithian dioxides (Bell and Bennett, *J.*, 1927, 1788). In order to demonstrate this the oxidation of 1 : 4-diphenylpiperazine has been examined. Hydrogen peroxide in acetone



or glacial acetic acid yielded as the main product the α-*dioxide*, crystallising magnificently from warm water as the *octahydrate*, which, however, rapidly effloresces to the *dihydrate* stable in air. Both hydrates lose their water in a vacuum to give the hygroscopic anhydrous *dioxide*.

From the mother-liquor of the α-dioxide a small quantity of a much more soluble β-*dioxide* was isolated which was found on analysis to have the composition β-dioxide,$H_2O_2,2H_2O$. The presence of hydrogen peroxide was also confirmed by direct tests. These crystals are stable in air and lose neither water nor hydrogen peroxide when kept in a vacuum. Both dioxides are readily reduced to the parent diphenylpiperazine.

The two dioxides give salts which are generally anhydrous and contain no hydrogen peroxide. Pairs of isomeric *hydrochlorides*, *nitrates*, and *picrates* were characterised and in addition the *sulphate*, *oxalate*, *perchlorate*, *ferrocyanide*, *platinichloride*, and *aurichloride* of the α-dioxide.

The two dioxides and all their salts decompose explosively when heated. A study of the temperatures of decomposition showed that for each substance explosion occurred after a particular time (t secs.) of heating at a given temperature (T °K.) where $\log_{10} t = a/T - b$, a and b being constants for the substance. This relationship is illustrated in the figure for observations with the α- and the β-nitrate and with the two dioxides (α-dioxide dihydrate and hydrated β-dioxide–hydrogen peroxide complex). The constants a and b for all the compounds studied are in the table.

Substance.	$10^{-4}a$.	b.	Temperature (° c.) (calc.) for $t = 1$ sec.
α-Oxalate	6·6	11·8	289°
α-Hydrochloride	5·7	10·6	268
α-Aurichloride	4·8	10·6	182
α-Nitrate	4·2	8·3	234
β-Nitrate	4·2	8·5	224
α-Picrate	6·5	13·5	221
β-Picrate	5·8	12·2	207
α-Dioxide dihydrate	3·2	5·8	281
β-Dioxide complex	5·8	12·0	210

It is noticeable that the values of a (slopes of the curves in the figure) are similar for the pairs of isomerides. This is not so for the two dioxides, but the compounds actually examined were in this case not isomeric since only the β-specimen contained combined hydrogen peroxide.

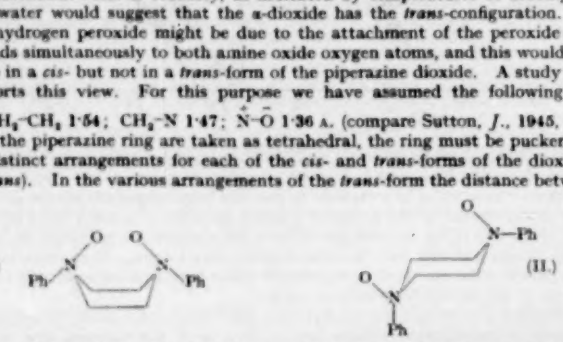
This type of behaviour has been reported more than once before, for example for the decomposition of lead styphnate (Hales, *Trans. Faraday Soc.*, **1933**, **29**, 544) and of barium azide (Hervey, *ibid.*, p. 653). The former author records some variation in times before detonation with the size of the crystals. Our specimens were all finely powdered.

These observations help in characterising the compounds examined and, in the absence of melting points, provide clear evidence of the individuality of the pairs of isomerides studied.

The α-dioxide and its salts are all somewhat more stable than their β-isomerides. The α-dioxide is more sparingly soluble in water (by a factor of the order of 100 : 1) than the β-dioxide, but in 95·6% alcohol the converse is true and the solubilities at 25° were α- 9·1 and β- 1·16% by weight.

Although the α-dioxide forms stable salts of the composition B,2HX, its aqueous solutions are not alkaline but have a pH between 6 and 7. Moreover measurably more N/10-sodium hydroxide is needed to change the colour of phenolphthalein in its presence than in pure water. A similar faintly acidic character was observed by Polonovski, Boulanger, and Taghavi (*Atti del X° Congresso Internazionale di Chimica, Roma*, 15—21, Maggio, 1938, XVI, **3**, 303) with dimethylpiperazine dioxide. The formula suggested by these authors for a negative ion produced by the union of an amine oxide and a hydroxyl ion is, however, electronically unsound and we doubt whether the effect under consideration can be explained in terms of normal bonding.

The tenacity with which the molecule of hydrogen peroxide is retained by the β-dioxide is remarkable and may be regarded as significant in connexion with the question of configuration. General considerations such as stability, as indicated by temperatures of decomposition, and solubility in water would suggest that the α-dioxide has the *trans*-configuration. The stable retention of hydrogen peroxide might be due to the attachment of the peroxide molecule by hydrogen bonds simultaneously to both amine oxide oxygen atoms, and this would be expected to be possible in a *cis*- but not in a *trans*-form of the piperazine dioxide. A study of molecular models supports this view. For this purpose we have assumed the following interatomic distances : CH_2–CH_2 1·54; CH_2–N 1·47; $\overset{+}{N}$–$\overset{-}{O}$ 1·36 A. (compare Sutton, *J.*, 1945, 146). If all the angles in the piperazine ring are taken as tetrahedral, the ring must be puckered and there are several distinct arrangements for each of the *cis*- and *trans*-forms of the dioxide (actually 5 *cis* and 4 *trans*). In the various arrangements of the *trans*-form the distance between the two



oxygen atoms is of the order 4—5 A., but in every case the bulky phenyl group or the atoms of the ring are interposed making any bridging by the hydrogen peroxide molecule improbable. On the other hand no such obstruction arises in the various arrangements of the *cis*-dioxide. In one of these (I) the oxygen atoms are less than 2 A. apart (calculated on the above-mentioned assumptions, 1·61 A.), but this particular arrangement would presumably have low stability owing to the close approach of the mutually repellent fields of the two amine oxide groups. The other possible arrangements of the *cis*-dioxide have oxygen atoms at a distance of the order 4—5 A., for example (II) (calculated distance, 4·35 A.). In considering the possible attachment

of hydrogen peroxide the *X*-ray examination of the crystal structure of the urea–hydrogen peroxide compound by Lu, Hughes, and Giguère (*J. Amer. Chem. Soc.*, 1941, **63**, 1507) is relevant. These authors concluded that the crystal is an assemblage of urea and hydrogen peroxide molecules held together by hydrogen bonds, the hydrogen peroxide molecule retaining the configuration calculated for it by Penney and Sutherland (*Trans. Faraday Soc.*, 1934, **30**, 898) in which the O–H bonds are at 101·5° to the O–O bond but lie in two planes inclined at 106° to each other. A trial with models, taking the O–O distance in hydrogen peroxide to be 1·47 A. (Giguère and Schomaker, *J. Amer. Chem. Soc.*, 1943, **65**, 2025) shows that this hydrogen peroxide molecule can in fact be fitted, with only slight distortion of the angles, to bridge the two oxygen atoms of the *cis*-dioxide in the arrangement (II) with hydrogen bond distances of the order 2·7 A. We therefore conclude that the stability of the hydrogen peroxide complex is strong evidence that the β-dioxide has the *cis*-configuration.

It is evident that the dioxide of dimethylpiperazine should similarly occur in *cis*- and *trans*-forms. Although this substance was described by Polonovski, Boulanger, and Taghavi (*loc. cit.*) no such isomerism was reported. Yet their paper does contain indications of the existence of two forms, and the point requires re-investigation.

While this work was in progress the geometrical isomerism of some diquaternary salts of dimethylpiperazine of the type $\left[RMeN\overset{CH_2\cdot CH_2}{\underset{CH_2\cdot CH_2}{\diagup\diagdown}}\overset{+}{N}MeR\right]X_2$ was described by Hanby and Rydon (*J.*, 1945, 833). These are analogous to the isomerides described in this paper.

Experimental.

Analyses.—Determinations of carbon, hydrogen, and nitrogen were made by Messrs. Weiler and Strauss. Determinations of peroxidic oxygen were carried out by the method recently described by one of us (Glynn, *Analyst*, 1947, **72**, 248). Explosion temperatures given below are calculated temperatures at which explosion occurs after 1 second.

Oxidation of 1 : 4-*Diphenylpiperazine.*—A mixture of the base (20 g.) dissolved in glacial acetic acid (300 ml.) with hydrogen peroxide (120 g. of 30% aqueous) was kept at 50—70° for 16 hours. The resulting dark red solution gave a copious precipitate of the α-dioxide when neutralised with 10*N*-sodium hydroxide, but in order to isolate the whole of the products with a minimum contamination with inorganic matter the solution was diluted and evaporated several times at 60° and finally kept over sodium hydroxide in a desiccator until all the acetic acid had been removed. The crude product had a peroxidic oxygen content of 6·8%. This was dissolved in water (500 ml.) at 60°, and the solution on cooling deposited crystals of the hydrated α-dioxide (15 g.). After 2 further crystallisations from water the *diphenylpiperazine α-dioxide octahydrate* was obtained in large well-formed crystals (Found : peroxidic O, 7·78, 7·68%).

Evaporation of the original mother-liquors yielded further small crops of crude α-dioxide, and the solution was finally taken to dryness in a desiccator over potassium hydroxide. A brown oily residue was left which gradually became crystalline (Found, in the crude product : peroxidic O, 13·2, 12·1%). This material was extracted with rectified alcohol, some insoluble inorganic matter being rejected, and after repeated crystallisation from 95% ethanol (charcoal) the β-dioxide was obtained.

Diphenylpiperazine α-Dioxide.—The large crystals from warm water are the octahydrate which effloresces rapidly in air (Found : C, 47·3; H, 8·0; N, 6·8. $C_{16}H_{16}O_2N_2,7{\cdot}7H_2O$ requires C, 47·2; H, 8·3; N, 6·9%. A freshly prepared specimen gave peroxidic O, 7·76; loss over P_2O_5, 34·9. $C_{16}H_{16}O_2N_2,8H_2O$ requires peroxidic O, 7·73; H_2O, 34·8%). This substance is sparingly soluble in cold water but more readily soluble in alcohol. 60 Ml. of a 0·16*M*-solution required 0·26 ml. of *N*/10-sodium hydroxide for titration with phenolphthalein as indicator, as compared with one drop in a similar volume of pure water.

This octahydrate crystallises magnificently in the orthorhombic system with $a : b : c = 0{\cdot}5639 : 1 : 0{\cdot}7067$. The habit is prismatic with the form $q(011)$ elongated along the c axis, the prisms being terminated by the form $m(110)$. Barker classification angles : $cq(001) : (101) = 51°25'$; $am(100) : (110) = 29°25'$; and $bq(010) : (011) = 54°45'$. The extinction is straight on the prism faces and one optic axis emerges nearly perpendicular to m.

The anhydrous *diphenylpiperazine α-dioxide* is obtained as a white hygroscopic powder by dehydrating the octahydrate *in vacuo* over phosphoric anhydride (Found : C, 69·8; H, 6·9. $C_{16}H_{16}O_2N_2$ requires C, 71·1; H, 6·5%). Exposed to the atmosphere this substance absorbs water (2 mols.) smoothly in 2 hours without any intermediate break in the process. The *dihydrate* so obtained is also formed by the efflorescence of the octahydrate in air (Found : C, 62·7; H, 7·25; N, 9·4; peroxidic O, 10·2%. $C_{16}H_{16}O_2N_2,2H_2O$ requires C, 62·7; H, 7·25; N, 9·2; peroxidic O, 10·4%). It is quite stable in air and is obtained in well-formed crystals when any of the forms of the α-dioxide is recrystallised from 95% ethanol. It explodes at 281° (corr.). Its solubility in 95·6% alcohol at 25° is 9·15 wt.-% of anhydrous dioxide.

The crystals of dihydrate belong to the holohedral class of the monoclinic system with $a : b : c = 2{\cdot}041 : 1 : 1{\cdot}500$ and $\beta = 87°4'$. The habit is usually tabular with $c(001)$ large, $a(100)$ absent or small, and the pyramid faces $o(111)$ and $p(\bar{1}11)$ prominent. Barker classification angles : $cr(001) : (101) = 35°15'$; $ra(101) : (100) = 51°49'$; $am(100) : (110) = 63°52'$ and $bq(010) : (011) = 33°43'$. The extinction on c is diagonal.

Reduced in aqueous hydrochloric acid with zinc dust the α-dioxide dihydrate yields the parent diphenylpiperazine base.

The *dihydrochloride* forms a colourless crystalline powder readily soluble in cold water but sparingly in alcohol and exploding at 266° (corr.) (Found: C, 55·1; H, 5·5; N, 8·7; HCl by titration, 21·4. $C_{18}H_{20}O_3N_2Cl_2$ requires C, 55·1; H, 5·8; N, 8·2; HCl, 21·3%). The *sulphate* is a white microcrystalline powder sparingly soluble in cold water or alcohol (Found: C, 52·1; H, 5·4; H_2SO_4 by titration, 26·9. $C_{18}H_{20}O_3N_2S$ requires C, 52·3; H, 5·4; H_2SO_4, 26·6%). The *dipicrate* crystallises from alcohol in yellow needles with a straight extinction, sparingly soluble in alcohol but more so in water, and exploding at 221° (corr.) (Found: C, 46·2; H, 3·4; N, 15·0. $C_{30}H_{24}O_{16}N_8$ requires C, 46·2; H, 3·3; N, 15·4%). The *dinitrate* is a white powder consisting of microscopic prismatic crystals having a high double refraction and an oblique extinction. It is sparingly soluble in water and explodes at 234° (corr.) (Found: C, 48·3; H, 4·7; N, 15·3. $C_{18}H_{20}O_9N_4$ requires C, 48·5; H, 5·1; N, 14·2%). The *oxalate* is a white microcrystalline powder sparingly soluble in cold water and exploding at 289° (corr.) (Found: C, 59·4; H, 5·5. $C_{18}H_{20}O_4N_2$ requires C, 59·8; H, 5·6%). The *monoperchlorate* was obtained, even in presence of an excess of perchloric acid, as a sparingly soluble microcrystalline powder exploding with a bright flash when heated (Found: C, 51·0; H, 4·8; N, 7·6; $HClO_4$ by titration, 27·5. $C_{18}H_{19}O_8N_2Cl$ requires C, 51·8; H, 5·2; N, 7·6; $HClO_4$, 27·1%). The *platinichloride* is a yellow sparingly soluble precipitate (Found: Pt, 28·6. $C_{18}H_{20}O_3N_2Cl_6Pt$ requires Pt, 28·7%). The *aurichloride* was obtained as a sparingly soluble yellow precipitate when gold chloride solution was added to the aqueous solution of the α-dioxide whether neutral or acid. It decomposes explosively at 182° (corr.) (Found: C, 31·4; H, 3·3; Cl, 22·2; Au, 32·9, 32·2. $C_{18}H_{21}O_3N_2Cl_4Au$ requires C, 31·6; H, 3·1; Cl, 23·2; Au, 32·3%). On the other hand, when the solution of the α-dioxide was added to an excess of gold chloride in aqueous hydrochloric acid, the precipitate, although very little different in composition (Found: Au, 31·7%), was extremely explosive, detonating on scratching or on heating to 90°. For analysis it was moistened and treated with sulphur dioxide, then dried, and ignited. The *ferrocyanide* forms sparingly soluble yellow needles with a straight extinction, which appear to be a dihydrate (Found: C, 56·7; H, 5·6; N, 17·9. $C_{38}H_{44}N_8O_4Fe$ requires C, 57·5; H, 5·7; N, 17·7%).

Diphenylpiperazine β-Dioxide.—The substance isolated from the final mother-liquors of the crystallisation of the crude dioxides crystallised from water in tufts of hair-like crystals or bunches of radiating prismatic needles and proved to be a *dihydrated hydrogen peroxide complex* of the β-dioxide (Found: C, 56·4, 56·7; H, 6·5, 6·7; N, 8·0. $C_{18}H_{24}O_4N_2$ requires C, 56·5; H, 7·1; N, 8·2%. A tetrahydrate of the β-dioxide would require C, 56·4; H, 7·1; N, 8·2%). This substance is many times as soluble in water as the α-isomeride. 95·6% Alcohol at 25° dissolves 1·16 wt.-% of it. It explodes at 210° (corr.) and remains unchanged when kept *in vacuo* over phosphoric anhydride.

The presence of molecular hydrogen peroxide in this compound was confirmed by direct tests. The material available being insufficient for repeated precise reductometric analysis by our usual procedure, two experiments were made as follows. (*a*) 10 Mg. each of the α-dioxide dihydrate and the β-dioxide complex were separately distilled with aqueous 1% sulphuric acid. The distillate from the β-specimen gave a positive reaction for peroxide with iodide and starch whereas that from the α-dioxide did not. (*b*) 10 Mg. each of the α-dioxide dihydrate and of the β-dioxide complex were separately dissolved in aqueous sulphuric acid (5 ml. of 2*N*.) in a stream of nitrogen, and 1 ml. of 5% potassium iodide and 1 ml. of 1% starch solution added to each. The β-dioxide complex gave an instantaneous blue colour; the α-dioxide developed a blue colour when kept. Both were then very slowly titrated with *N*/10-thiosulphate. The α-dioxide required 1·40 ml., the β-dioxide complex 2·15 ml. of thiosulphate solution. The latter thus has a content of total peroxidic oxygen 50% higher than the former corresponding to the presence of one mol. of hydrogen peroxide in the latter.

The β-dioxide complex was reduced by zinc dust in acid solution to the parent diphenylpiperazine.

The following salts of the β-dioxide were prepared: the *dipicrate*, small yellow needles with a high double refraction and a straight extinction, which explode at 207° (corr.) (Found: C, 46·1; H, 3·4; N, 15·2. $C_{30}H_{24}O_{16}N_8$ requires C, 46·2; H, 3·3; N, 15·4%); the *dihydrochloride*, a white microcrystalline powder (Found: C, 55·4; H, 6·1; N, 7·7. $C_{18}H_{20}O_3N_2Cl_2$ requires C, 55·1; H, 5·8; N, 8·2%); the *dinitrate*, colourless thin plates, rhomb-shaped or elongated with oblique ends, having low double refraction and an oblique extinction, which explode at 224° (corr.) (Found: C, 48·2; H, 5·3. $C_{18}H_{20}O_9N_4$ requires C, 48·5; H, 5·1%). The β-dioxide also yields an aurichloride, a sulphate, and a perchlorate more soluble in alcohol than the α-salts.

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50. *The Infra-red Spectra of Carcinogens. Part I. Derivatives of Stilbene.*

By H. W. Thompson, Eva E. Vago, M. C. Corfield, and S. F. D. Orr.

A survey has been made of the vibrational spectra of some carcinogens. This paper describes results for derivatives of stilbene. The spectra provide data which may be useful for analytical work, and correlations have been drawn up between important spectral features and the individual molecular structures. By use of such correlations it may be possible to identify the type of substitution in aromatic rings existing in such compounds.

The main purposes of this investigation were (*a*) to begin a comprehensive survey of the infra-red absorption spectra of complex molecules which are important in the field of cancer research, and (*b*) to correlate spectral features with molecular structure in related series of

molecules in which structural alterations are known to affect carcinogenic activity (Haddow, *Brit. Med. Bull.*, 1947, **4**, 331; Haddow, Harris, Kon, and Roe, *Phil. Trans.*, 1948, **241**, 147). We were stimulated to carry out this programme by discussions with the staff of the Chester Beatty Research Institute, from whom we have obtained most of the compounds examined. The compilation of the spectra of these compounds may well form a valuable basis for analytical work, such as has been developed for urinary keto-steroids by Dobriner, Liebermann, Rhoads, Williams, and Barnes (*J. Biol. Chem.*, 1948, **172**, 247). As regards structural diagnosis, much is now known about the correlation of certain absorption bands with particular atomic groupings (Thompson, *J.*, 1948, 328; Williams, *Rev. Sci. Instr.*, 1948, **19**, 135), and as more reference data have accumulated it has been found that the characteristic vibration frequencies of some groups may be affected by special electronic influences introduced by neighbouring substituents or structural factors. This has been illustrated clearly by the work on the steroids already mentioned (Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2024). The present paper summarises results for some derivatives of stilbene.

Experimental Method.

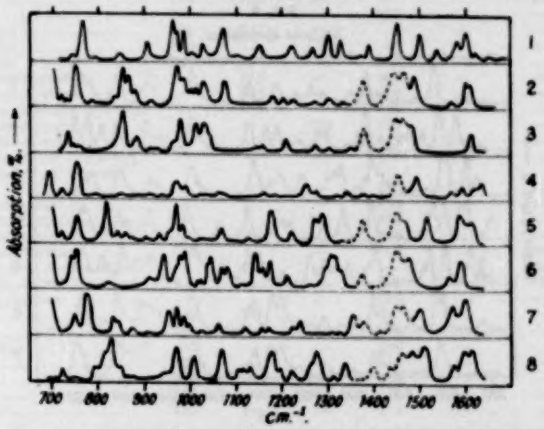
The spectra were measured between 5 and 15 μ. using the powdered solids ground to a paste with paraffin and pressed between rock-salt plates. Between 7 and 15 μ. a single-beam recording spectrometer was used with a rock-salt prism, and between 5 and 8 μ., where the absorption of atmospheric water vapour is strong, a double-beam recorder with a calcium fluoride prism was used. A few of the spectra were measured on a Perkin Elmer 12 C instrument with a rock-salt prism. The effective slit widths were about 5 cm.$^{-1}$ over the whole range. Unfortunately in the region 6·5—7·5 μ. there are paraffin absorption bands, and also, when the paste is used, scattering errors lead to inexact balancing of the double-beam recorder. For this reason some of the curves recorded over this range are uncertain, but no bands of major interest are to be expected here.

Results and Discussion.

The spectra are shown in Figs. 1—4. An experimental result of general interest was that with some of these compounds the Christiansen effect was observed as described recently for

FIG. 1.

Stilbene and derivatives.



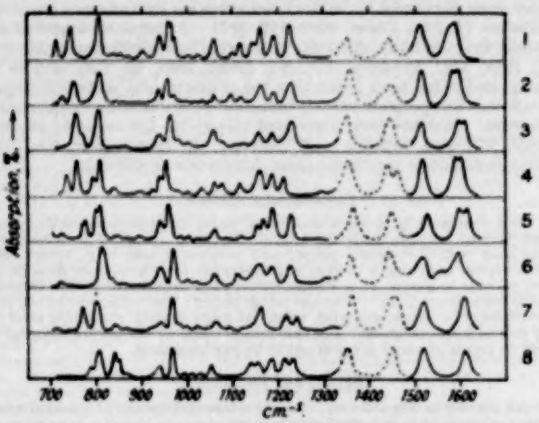
(1) *Stilbene.* (2) 2 : 4 : 6-*Trimethylstilbene.* (3) 2 : 4 : 6 : 2′ : 4′ : 6′-*Hexamethylstilbene.* (4) 2-*Aminostilbene.* (5) 4-*Aminostilbene.* (6) 2-*Dimethylaminostilbene.* (7) 3-*Dimethylaminostilbene.* (8) 4′-*Bromo*-4-*dimethylaminostilbene.*

other slurries by Price and Tetlow (*J. Chem. Phys.*, 1948, **16**, 1157). This was clearly detectable by the very rapid changes of transmission coefficient near certain absorption bands. It may be significant that, in most cases of 4-dimethylaminostilbenes where it occurred, the phenomenon was particularly marked at about 1190 cm.$^{-1}$ (8·4 μ.), but several absorption bands in the same spectrum were usually affected.

The spectra shown in the figures reveal differences between the isomeric compounds and between related homologues which may be useful for analytical work.

FIG. 2.

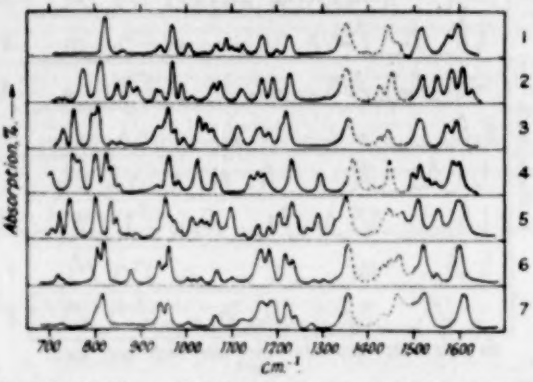
Stilbene derivatives.



(1) *4-Dimethylaminostilbene.* (2) *4-Dimethylamino-2'-methylstilbene.* (3) *4-Dimethylamino-2'-ethylstilbene.* (4) *4-Dimethylamino-2'-isopropylstilbene.* (5) *4-Dimethylamino-3'-methylstilbene.* (6) *4-Dimethylamino-4'-methylstilbene.* (7) *4-Dimethylamino-2' : 6'-dimethylstilbene.* (8) *4-Dimethylamino-2' : 4' : 6'-trimethylstilbene.*

FIG. 3.

Stilbene derivatives.

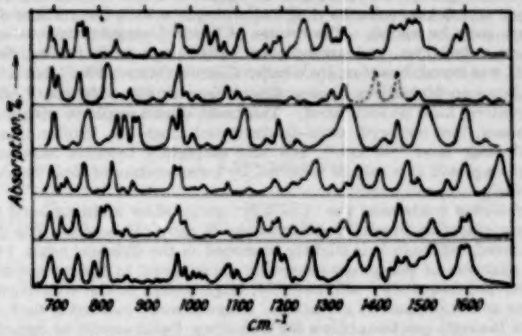


(1) *4'-Chloro-4-dimethylaminostilbene.* (2) *3'-Bromo-4-dimethylaminostilbene.* (3) *2'-Chloro-4-dimethylaminostilbene.* (4) *2-Chloro-4-dimethylaminostilbene.* (5) *4-Dimethylamino-2 : 2'-dimethylstilbene.* (6) *4-Dimethylamino-2' : 4'-dimethylstilbene.* (7) *4 : 4'-Bisdimethylaminostilbene.*

Characteristic spectral features are to be expected of (*a*) the substituted aromatic nuclei, and (*b*) the ⁻CH=CH⁻ group. Of the former, perhaps the most striking is that which originates in the deformation of residual C⁻H bonds out of the plane of the substituted aromatic ring to which they are attached (Whiffen and Thompson, *J.*, **1945**, 268; Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 246; Bell, Thompson, and Vago, *Proc. Roy. Soc.*, **1948**, *A*, **192**,

FIG. 4.

Stilbene derivatives.



(1) 2-*Methoxystilbene.* (2) 4-*Bromostilbene.* (3) 4-*Nitrostilbene.* (4) 4-*Acetylstilbene.* (5) 4-*Ethylaminostilbene.* (6) 4-*Diethylaminostilbene.*

TABLE I.

Characteristic vibration frequencies of different types of substituted stilbene derivatives.

Stilbene derivative.	Type of substitution, Mono.	di. *o*.	di. *m*.	di. *p*.	tri. 1 : 2 : 3.	tri. 1 : 2 : 4.	tetra. 1 : 2 : 3 : 5.
2 : 4 : 6-Trimethyl	750	—	—	—	—	—	852
2 : 4 : 6 : 2′ : 4′ : 6′-Hexamethyl	—	—	—	—	—	—	851
2-Amino	752	752	—	—	—	—	—
4-Amino	750	—	—	818	—	—	—
2-Dimethylamino	740	752	—	—	—	—	—
3-Dimethylamino	750	—	775	—	—	—	—
4-Dimethylamino	747	—	—	810	—	—	—
4-Dimethylamino-2′-methyl	—	752	—	809	—	—	—
4-Dimethylamino-2′-ethyl	—	757	—	809	—	—	—
4-Dimethylamino-2′-*iso*propyl	—	757	—	809	—	—	—
4-Dimethylamino-3′-methyl	—	—	778	810	—	—	—
4-Dimethylamino-4′-methyl	—	—	—	816	—	—	—
4-Dimethylamino-2′ : 6′-dimethyl	—	—	—	805	772	—	—
4-Dimethylamino-2′ : 4′ : 6′-trimethyl	—	—	—	807	—	—	845
4′-Chloro-4-dimethylamino	—	—	—	822	—	—	—
3′-Bromo-4-dimethylamino	—	—	772	812	—	—	—
2′-Chloro-4-dimethylamino	—	755	—	809	—	—	—
2-Chloro-4-dimethylamino	755	—	—	—	—	802	—
4-Dimethylamino-2 : 2′-dimethyl	—	746	—	—	—	803	—
4-Dimethylamino-2′ : 4′-dimethyl	—	—	—	821	—	807	—
4 : 4′-Bisdimethylamino	—	—	—	816	—	—	—
2-Methoxy	755	755	—	—	—	—	—
4-Bromo	750	—	—	814	—	—	—
4′-Bromo-4-amino	—	—	—	830	—	—	—
4-Nitro	766	—	—	835	—	—	—
4-Acetyl	762	—	—	824	—	—	—
4-Ethylamino	750	—	—	810	—	—	—
4-Diethylamino	750	—	—	812	—	—	—

498). Intense bands occur in the region 700—900 cm.$^{-1}$ according to the number and position of substituents in the aromatic nucleus. Two other vibrations of the aromatic nucleus near 1500 cm.$^{-1}$ and 1600 cm.$^{-1}$ frequently occur, but their intensities, both absolute and relative to each other, are variable. The C–H out-of-plane vibrations in the present series of compounds fall into line well with the earlier deductions. Table I summarises the data, from which it is seen that with few exceptions the different substitution types have vibration frequencies lying close to fixed values, *e.g.*, *ortho*-derivatives near 755 cm.$^{-1}$, *meta* near 775 cm.$^{-1}$, *para* from 805 to 820 cm.$^{-1}$, 1 : 2 : 4-trisubstituted derivatives near 805 cm.$^{-1}$, and 1 : 2 : 3 : 5-

tetrasubstituted derivatives near 850 cm.$^{-1}$. The conjugation of highly polar groups such as NO_2 or $CO{\cdot}CH_3$, causes some displacement of frequencies, but this occurs also in simpler compounds when such groups are attached to single benzene nuclei. It therefore seems possible to use such correlation rules for diagnostic purposes with the stilbene derivatives. A further refinement may be added. The results of Table I suggest that an ambiguity may arise between monosubstituted and *ortho*-disubstituted rings, both having the strong band near 750 cm.$^{-1}$. It was found, however, by Whiffen (Thesis, Oxford, 1946) that a large variety of monosubstituted benzene derivatives have a strong band at 690—700 cm.$^{-1}$, whilst the *ortho*-disubstituted derivatives have no such band. This band, occurs similarly with monosubstituted rings in the stilbenes, but not with *ortho*-disubstituted rings. A similar band occurs with *meta*-disubstituted rings near 700 cm.$^{-1}$, but any ambiguity between monosubstituted and *meta*-disubstituted rings will as a rule be removed by consideration of their bands near 750 and 775 cm.$^{-1}$, respectively.

The spectra of olefins containing the $-CH{=}CH-$ group show a strong band near 965 cm.$^{-1}$ which arises from a vibration involving deformation of the C–H bonds. This occurs with all the stilbenes measured, although it is slightly displaced in the different cases. Any alteration in the electronic structure of this group caused by substituents in the phenyl nuclei might be expected to modify the frequency; alternatively, large groups in the *ortho*-positions might so affect the structure as to influence its vibration. There is some indication that the presence of blocking-groups in the *ortho*-positions raises the frequency, but it cannot be regarded as definite.

One question upon which the present results give no guide is the coplanarity or otherwise of the two phenyl nuclei. The possible connexion between this and carcinogenic activity has been discussed by Haddow, Harris, Kon, and Roe (*loc. cit.*). It seems possible that, by use of the rules given above for the identification of particular nuclei substituted in different ways, the study of single crystals with polarised radiation and the reflecting microscope (Barer, Cole, and Thompson, *Nature*, 1949, **163**, 198) may throw further light on this.

Another general matter is being examined, namely, the effect of the state of aggregation on the spectra. There are signs of small shifts in the positions of some bands on changing from solids to solutions, and this may to some extent affect the application of structural diagnosis.

We are most grateful to Prof. G. A. R. Kon, F.R.S., for the specimens of aminostilbenes examined.

The Physical Chemistry Laboratory, Oxford. [*Received, June 30th*, 1949.]

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51. *The Infra-red Spectra of Carcinogens. Part II. Polynuclear Hydrocarbons.*

By S. F. D. Orr and H. W. Thompson.

Vibration spectra of some polynuclear aromatic hydrocarbons, which are of interest in cancer research, have been measured. Attempts have been made to correlate spectral features with molecular structure, particularly with regard to the vibrations of C—H bonds in substituted aromatic rings.

In continuation of work described in the preceding paper, we now give results for the spectra of some polynuclear hydrocarbons and a few related molecules. As before, the data may be useful for analytical work, and as regards the correlation of spectrum with molecular structure it was interesting to discover how far the rules given in the previous paper for the identification of aromatic nuclei substituted in different positions are applicable when the substituent bonds are themselves part of other rings of the ring-system.

The experimental methods were as described in the preceding paper, except that most of the spectra were measured on a Perkin Elmer 12 C spectrometer, with a prism of rock salt or lithium fluoride. The compounds were measured as thin solid films made by melting a small sample and pressing it between rock-salt plates. In the case of 9 : 10-dihydroanthracene, which tends to decompose on melting, a paste in paraffin was used.

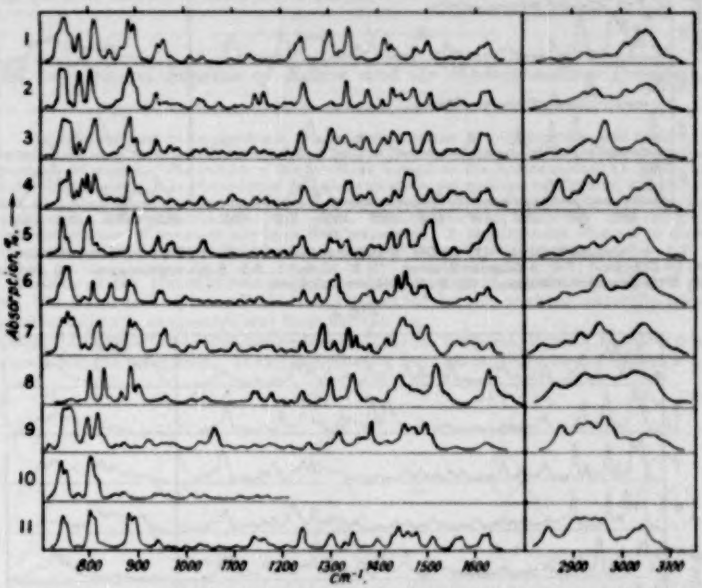
The spectra are shown in Figs. 1, 2, and 3. The broad features of the spectra of the 1 : 2-benzanthracenes (Fig. 1) are a number of strong bands between 700 and 900 cm.$^{-1}$, a region of comparative transparency at 900—1200 cm.$^{-1}$, and a complex arrangement of bands between 1200 and 1700 cm.$^{-1}$. The vibrations giving rise to the intense bands at 700—900 cm.$^{-1}$ will include the out-of-plane deformations of C—H bonds in the substituted aromatic rings. It

is clear that in the present set of compounds the situation is more complex than with the stilbenes described in the preceding paper, but several points emerge.

All the compounds in Fig. 1, except 2' : 6-dimethyl-1 : 2-benzanthracene, contain an aromatic ring which is 1 : 2-disubstituted only. It is therefore noticeable that all except this compound have a strong band around 750 cm.$^{-1}$, in the characteristic position for an *ortho*-disubstituted ring, although the small shift from one molecule to another is rather bigger than usual. This rule for 1 : 2-disubstitution also appears to hold for the other compounds in Figs. 2 and 3, except 9 : 10-dihydroanthracene and anthracene itself, but in many cases there is a shift of 10 cm.$^{-1}$ to higher or lower frequencies.

FIG. 1.

1 : 2-*Benzanthracenes.*



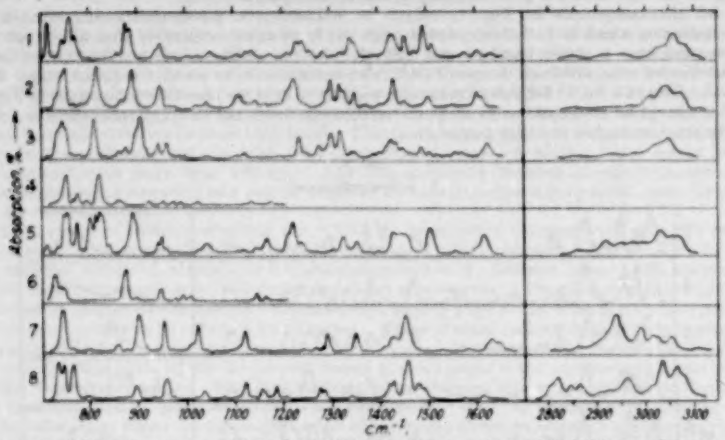
(1) 1 : 2-*Benzanthracene.* (2) 5-*Methyl*-1 : 2-*benzanthracene.* (3) 5-*Ethyl*-1 : 2-*benzanthracene.* (4) 5-n-*Propyl*-1 : 2-*benzanthracene.* (5) 7-*Methyl*-1 : 2-*benzanthracene.* (6) 9-*Methyl*-1 : 2-*benzanthracene.* (7) 1'-*Methyl*-1 : 2-*benzanthracene.* (8) 2' : 6-*Dimethyl*-1 : 2-*benzanthracene.* (9) 9 : 10-*Dimethyl*-1 : 2-*benzanthracene.* (10) 6 : 9 : 10-*Trimethyl*-1 : 2-*benzanthracene.* (11) 5 : 6-cyclo*Penteno*-1 : 2-*benzanthracene.*

Another noticeable characteristic of the benzanthracenes (Fig. 1) is a strong band near 890 cm.$^{-1}$, which occurs in all cases unless there is substitution also in the 9 : 10-positions. This suggests that the central ring can be regarded as being substituted in the 1 : 2 : 4 : 5-positions. For ordinary 1 : 2 : 4 : 5-tetrasubstituted benzene derivatives, a band has previously been found at about 875 cm.$^{-1}$. It should be noted however that 9-methyl-1 : 2-benzanthracene has a weaker band at 890 cm.$^{-1}$. Among the other compounds of Figs. 2 and 3 with one exception all those with an unsubstituted middle anthracene ring show the band near 890 cm.$^{-1}$, and with one exception it is absent from molecules with essentially different structures, such as a reduced middle anthracene ring. The exception is again 9 : 10-dihydroanthracene, which shows a band near 890 cm.$^{-1}$, although this is weaker than usual.

The other strong bands between 700 and 900 cm.$^{-1}$ are more difficult to correlate. One possible regularity is suggested by the strong bands at 800—810 cm.$^{-1}$ found in all compounds (except acridine derivatives) containing 1 : 2 : 3 : 4-substitution. Although simple 1 : 2 : 3 : 4-tetrasubstituted benzene derivatives have not been available to enable us to determine the

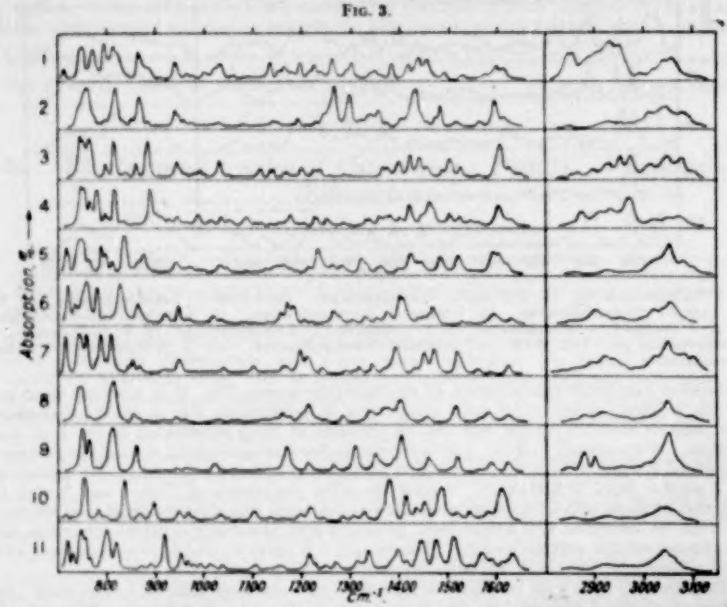
FIG. 2.

Dibenzanthracenes and anthracenes.



(1) 1 : 2-3 : 4-*Dibenzanthracene*. (2) 1 : 2-5 : 6-*Dibenzanthracene*. (3) 1 : 2-6 : 7-*Dibenzanthracene*. (4) 9 : 10-*Dihydro*-1 : 2-5 : 6-*dibenzanthracene*. (5) 3'-*Methyl*-1 : 2-5 : 6-*dibenzanthracene*. (6) *Anthracene*. (7) 2 : 3-*Dimethylanthracene*. (8) 9 : 10-*Dihydroanthracene*.

FIG. 3.



(1) 1 : 2-cyclo*Pentenophenanthrene*. (2) *Chrysene*. (3) 2-*Methyl*-3 : 4-*benzphenanthrene*. (4) 2-iso*Propyl*-3 : 4-*benzphenanthrene*. (5) 1 : 2-5 : 6-*Dibenzphenanthrene*. (6) 1 : 2-*Benzfluorene*. (7) 3 : 4-*Benzfluorene*. (8) 1 : 2-5 : 6-*Dibenzfluorene*. (9) 1 : 2-7 : 8-*Dibenzfluorene*. (10) 3 : 4-6 : 7-*Dibenzacridine*. (11) 1 : 2-8 : 9-*Dibenzacridine*.

characteristic C—H out-of-plane frequency in this type, we might argue by extrapolation from the results with the other compounds that it would have a value close to that just found.

A less prominent band which seems to persist throughout the 1 : 2-benzanthracenes lies near 1240 cm.$^{-1}$, although here a few small deviations occur which, taken with the weaker nature of the band, obscure the position.

In the region 2800—3100 cm.$^{-1}$ these compounds have bands due to the C—H stretching vibrations. Beyond the general and expected result that the aromatic C—H vibrations give bands at 3000—3100 cm.$^{-1}$ and the aliphatic C—H vibrations at lower frequencies, 2850—2950 cm.$^{-1}$, no very significant conclusions can at present be drawn.

We are again indebted to Prof. G. A. R. Kon, F.R.S., for most of the pure hydrocarbon examined.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, June 30th*, 1949.]

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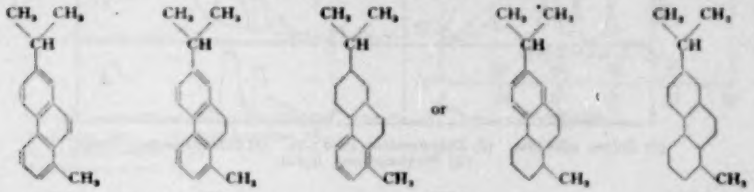
52. *Infra-red Studies of Retene and its Hydrogenation Products.*

By P. V. LAAKSO, S. F. D. ORR, and H. W. THOMPSON.

The infra-red absorption spectra of retene, dihydroretene, octahydroretene, and perhydroretene have been measured, between 3 and 15 μ. They have been used to provide analytical methods of studying the nature of the products formed in the hydrogenation of retene by different methods. It has been found that these products are confined to dihydro-, octahydro- and perhydro-retene, and this corresponds to the stability of these compounds in which only aromatic and fully saturated rings occur. Similar reactions involving the catalytic dehydrogenation of hydroretenes have been examined. A melting-point diagram is given for retene and dihydroretene, which form a complete series of mixed crystals.

THE presence of the phenanthrene nucleus in such important classes of compound as the sterols, bile acids, and certain alkaloids has prompted further work on naturally occurring polynuclear aromatic compounds and their derivatives.

Retene [1-methyl-7-*iso*propylphenanthrene (I)] is of particular interest in relation to the resin acids and the diterpenes. It can theoretically form seven hydroretenes, in which 2, 4, 6,



(I.) (II.) (III.) (IV.)

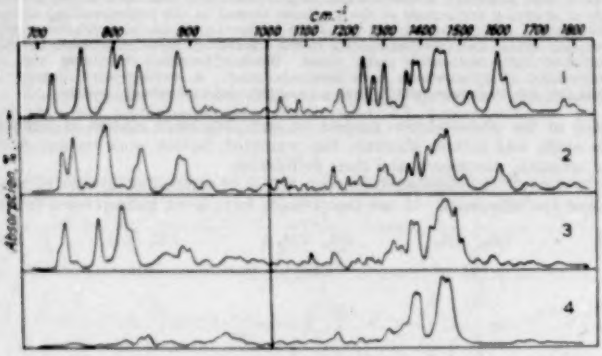
8, 10, 12, and 14 hydrogen atoms respectively have been added to the molecule. Retene and perhydroretene can each exist in only one form, but all the others are capable of structural isomerism. For example, there are theoretically 16 isomers of dihydroretene, depending on which bond has been saturated, and with the more fully hydrogenated derivatives the number of isomers is still greater. On theoretical grounds, the isomers may differ greatly in stability, and in practice dihydroretene is found only as the 9 : 10-compound (II), formed from retene either by catalytic reduction or by the action of sodium and amyl alcohol. On grounds of ring strain, the most stable derivatives would be expected to be dihydroretene, octahydroretene (III), and perhydroretene (IV). These derivatives should be formed preferentially in the catalytic reduction of retene. It has been shown, for example, that reduction of retene in presence of a nickel catalyst gives perhydroretene (Ipatiev, *Ber.*, 1909, **42**, 2095; Laakso, *Ann. Acad. Sci. Fennicæ*, 1949, *A*, No. 28), whilst if copper chromite is used a mixture of dihydroretene and octahydroretene is formed (Laakso, *loc. cit.*). Whenever the hydrogenation with a nickel catalyst is interrupted before the full complement of hydrogen has been taken up, a mixture of these particular hydroretenes and retene is obtained. Thus, if the equivalent of four hydrogen atoms has been absorbed, no tetrahydroretene is found but only retene and perhydroretene.

However, Bamberger and Lodter (*Ber.*, 1887, **20**, 3073) claimed to have prepared tetrahydroretene using sodium and amyl alcohol. Liebermann and Spiegel (*Ber.*, 1889, **22**, 779) similarly claimed to have prepared dodecahydroretene using phosphorus and hydrogen iodide, and Virtanen a whole series of hydroretenes by the same methods (*Ber.*, 1920, **53**, 1880). In these investigtions no chemical tests were given which characterised the products, which might have been mixtures. It therefore seemed appropriate to apply infra-red absorption spectroscopy to the problem, and the results have indeed substantiated the argument outlined above about the relative stability of the hydroretenes. Some analogous problems involved in the dehydrogenation of hydroretene have been examined by the same method.

The spectrometers used were automatic recorders, described in detail elsewhere (Thompson and Whiffen, *J.*, 1945, 269; Richards and Thompson, this vol., p. 124). A rock-salt prism was used for most of the work, but the region 2—7 μ. was also measured with prisms of calcium fluoride and lithium fluoride. The compounds were measured as thin solid layers melted on rock-salt plates, as liquids, or in dilute solutions in carbon tetrachloride or bromoform as indicated below.

The Hydrogenation of Retene.—The spectra of pure samples of retene, dihydroretene, octahydroretene, and perhydroretene were first determined for reference. These are shown in Figs. 1 and 2.

FIG. 1.



(1) *Retene, solid film.* (2) *Dihydroretene, solid film.* (3) *Octahydroretene, liquid.* (4) *Perhydroretene, liquid.*

Part of the spectrum of retene was previously recorded by Barnes, Gore, Liddel, and Williams (*Ind. Eng. Chem. Anal.*, 1943, **15**, 659). It is seen that well-marked differences exist between the spectra in several spectral regions, which serve to characterise the compounds, and it seems certain that other hydroretenes would have equally distinctive features.

Attempts were then made to prepare tetrahydro-, hexahydro-, octahydro-, and decahydroretene by the methods described by Virtanen. For tetrahydro-retene, retene was reduced by sodium in amyl alcohol in several ways, namely, (*a*) with a small amount of sodium and heating with an open flame, (*b*) with a larger amount of sodium and similar heating, (*c*) with a further excess of sodium, and (*d*) with an excess of sodium but heating in an oil-bath. The spectra of the products, and of distillation fractions from each of them, were then measured. In the first three cases, a moderately strong band, the originator of which appeared to become concentrated in the higher-boiling fractions, occurred at 1740 cm.$^{-1}$ and was attributed to a carbonyl group. This did not occur with material obtained by method (*d*) in which local over-heating was avoided, and the compound responsible for it, which could not have been present in great amount, can be confidently regarded as a by-product formed from amyl alcohol. All the other bands in the spectra could be satisfactorily accounted for as a mixture of two or more of those of retene, dihydroretene, and octahydroretene.

The more saturated hydroretenes were made by reduction of retene with phosphorus and

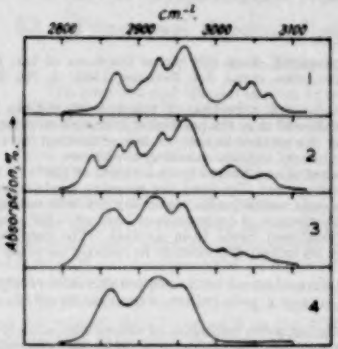
hydrogen iodide. In this case all the bands found in the spectra of the products were explicable in terms of retene, dihydroretene, octahydroretene, and perhydroretene. As the proportion of hydrogen taken up is increased, the more fully hydrogenated derivatives become more prominent, as might be expected.

It was found that the boiling point of the mixture of hydrogenation products did not vary gradually and continuously during a distillation, and this suggested the formation of azeotropic mixtures. It will be shown later that retene and dihydroretene form a complete series of mixed crystals.

Dehydrogenation of Hydroretenes.—When a sample of dihydroretene, which had been prepared by catalytic reduction of retene and purified by recrystallisation, was dehydrogenated with Raney nickel, it did not evolve the full equivalent of hydrogen, but about 10% less (Laakso, *Ann. Acad. Sci. Fennicæ*, 1949, *A*, No. 32). It had been suggested that this result might have arisen by disproportionation. The spectral examination of the sample of dihydroretene showed however that it contained a small amount of retene. By repeated recrystallisation, it was possible to prepare a specimen of dihydroretene, m. p. 56—58°, the spectrum of which was free from the bands of retene. Dihydroretene was found to become

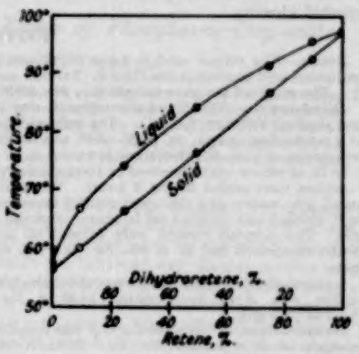
FIG. 2.

Solutions in carbon tetrachloride.



(1) *Retene*, 2%. (2) *Dihydroretene*, 2%.
(3) *Octahydroretene*, 2%.
(4) *Perhydroretene*, 1%.

FIG. 3.



concentrated in the mother-liquor rather than in the crystals, and the purest specimen was found in the last mother-liquor after fractional evaporation and filtration of the alcoholic solution. Retene and dihydroretene appear to form a complete series of mixed crystals, the melting point increasing as the percentage of retene increases (Fig. 3). The presence of retene in the sample of dihydroretene would account for the deficit of hydrogen in the dehydrogenation discussed above. Indeed, the gradual melting over 2° of the sample of dihydroretene thought to be pure suggests that about 1% of impurity may still be present, but the spectra show definitely that this impurity cannot be retene.

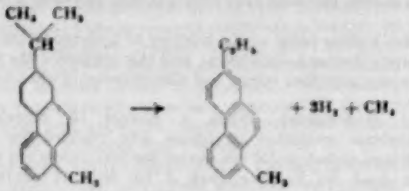
Simultaneously with the liberation of hydrogen in the dehydrogenation process, methane is formed. This presumably comes from a degradation of the *iso*propyl group, but spectral changes which might confirm this would be slight and have not been detected.

The dehydrogenation of octahydroretene has also been studied. With Raney nickel at 220° a smooth reaction occurs in which hydrogen is liberated, but in smaller amount than would be required for complete dehydrogenation. At the same time much methane is formed. These results can be explained by the occurrence of two reactions simultaneously with the straight dehydrogenation.

In the first, disproportionation leads to retene and perhydroretene:

$$2C_{18}H_{30} \longrightarrow C_{18}H_{18} + C_{18}H_{32} + H_2$$

and in the second, the isopropyl radical loses methane, subsequent dehydrogenation leading to 1-methyl-7-ethylphenanthrene :



The product obtained from the dehydrogenation of octahydroretene was found spectroscopically to show bands of retene and perhydroretene, and also other unexplained bands. The sample was then separated into a crystalline and an oily fraction. The former was almost pure retene; the latter contained much perhydroretene and also the unidentified component. Although the third component could not be completely identified from its spectral features, there is no doubt that it contains aromatic nuclei and methyl groups. It has not yet been possible to obtain a synthetic sample of 1-methyl-7-ethylphenanthrene to establish the expected identity.

Experimental.

Retene.—The retene used in these experiments was prepared, from the higher fractions of tar, by distillation and fractional distillation (Talvitie and Laakso, *Ann. Acad. Sci. Fennicæ*, 1946, *A*, No. 21, 10). The m. p. of the pure sample was 98—98·5°.

Dihydroretene.—The dihydro-compound was prepared by the reduction of retene with sodium in amyl alcohol (Virtanen, *loc. cit.*). The infra-red spectrum showed that the product still contained retene, but a retene-free sample, m. p. 56—58°, was isolated from the mother-liquor. A better method for the preparation of pure dihydroretene is to use more sodium, under slightly modified conditions.

10 G. of retene were dissolved in 100 c.c. of dry amyl alcohol and heated in an oil-bath at 130°. 8 G. of sodium were added during 2 hours. When all the sodium had dissolved the reaction mixture was poured into water, and the amyl alcohol layer separated and washed with water until it was neutral. Amyl alcohol was distilled off in steam, and the residual mixture of hydroretenes kept at −10° overnight. The crystals formed were filtered off and recrystallised twice from alcohol. The resultant dihydro-compound had m. p. 56—58°, and was shown by its infra-red spectrum to contain no trace of retene.

Octahydroretene.—This was prepared by catalytic reduction of retene with a copper chromite catalyst (Laakso, *Ann. Acad. Sci. Fennicæ*, 1949, *A*, No. 28). It was a pale yellow, very viscous oil, b. p. 101—102°/1·0 mm.

Perhydroretene.—This hydrocarbon was prepared by the catalytic reduction of retene with a nickel–kieselguhr catalyst (Laakso, *loc. cit.*). It was a colourless, not very viscous, oil, b. p. 332—335°/760 mm.

Preparation of "Tetrahydroretene."—(a) *With direct heating.* A solution of 10 g. of retene in 75 c.c. of amyl alcohol was heated to boiling on a wire-gauze, and 9 g. of sodium, cut into small pieces, were added during 2 hours. The mixture was poured into water, the amyl alcohol layer was separated, the solvents were removed by distillation, and "tetrahydroretene" was isolated as described by Virtanen, as a yellowish viscous oil, b. p. 180—183°/10 mm.

(b) *With excess of sodium and direct heating.* 10 G. of retene in 400 c.c. of amyl alcohol were heated to boiling on a wire-gauze. 25 G. of sodium, cut in small pieces, were added during 3 hours. Subsequent treatment was as in (a) above, three different fractions being collected during distillation under reduced pressure.

(c) *With excess of sodium and indirect heating.* The procedure was the same as in (b), but the flask was placed in an oil-bath heated to 130°. The product was distilled *in vacuo* three times, and two main fractions were taken. The first fraction (2·5 g.), b. p. 190—195°/1·0 mm., a yellow, viscous oil, was pure octahydroretene (Found : C, 89·5; H, 10·6. Calc. for $C_{18}H_{32}$: C, 89·2; H, 10·8%). The second fraction (3·0 g.), b. p. 220—223°/10 mm., a yellow viscous oil, gave analytical data corresponding to tetrahydroretene (Found : C, 90·5; H, 9·3. Calc. for $C_{18}H_{28}$: C, 90·7; H, 9·3%).

Reduction of Octahydroretene with Sodium.—5 G. of octahydroretene were dissolved in 100 c.c. of amyl alcohol and heated at 130° in an oil-bath. 10 G. of sodium, in small lumps, were added during 2 hours. Subsequent treatment, as in (a) above, gave 4 g. of a product, b. p. 190—195°/1·0 mm., which was a viscous, yellow oil, identical with the original sample of octahydroretene.

Preparation of "Hexahydroretene."—6 G. of retene, 7 g. of hydrogen iodide, and 3 g. of red phosphorus were heated in an atmosphere of carbon dioxide, in a sealed tube, so that the temperature rose to 200° during 3 hours. The tube was maintained at this temperature for 10 hours as described by Virtanen (*loc. cit.*). The product was boiled with water and extracted with ether, the ethereal extract was washed with water and dried (Na_2SO_4), the ether was evaporated, and the residue was distilled *in vacuo*. The fraction, b. p. 175—177°/10 mm., was collected, and its analysis found to correspond to that for "hexahydroretene" (Found : C, 90·1; H, 10·2. Calc. for $C_{18}H_{34}$: C, 89·9; H, 10·1%).

Preparation of Octahydroretene.—The procedure was the same as above, but the temperature was raised to 240° during 4 hours and was maintained at that level for 10 hours. The fraction, b. p.

163—165°/10 mm., was collected: its analysis corresponded to that of octahydroretene (Found: C, 89·1; H, 10·7. Calc. for $C_{18}H_{32}$: C, 89·2; H, 10·8%).

Preparation of Decahydroretene.—The procedure was again as above, but the temperature was raised to 285° during 4 hours and maintained for 10 hours. The fraction, b. p. 155—158°/750 mm., was collected and gave an analysis corresponding to decahydroretene (Found: C, 88·7; H, 11·2. Calc. for $C_{18}H_{32}$: C, 88·5; H, 11·5%).

Dehydrogenation of Dihydroretene.—1 G. of dihydroretene, m. p. 64—65°, and 0·3 g. of Raney nickel were heated, in a distillation flask connected to a gasometer, on an oil-bath at 220° until the evolution of gas had ceased. The dehydrogenation product was dissolved in ether and separated from the catalyst by filtration. It had m. p. 89—91°, raised by recrystallisation to 98—99°.

Dehydrogenation of Octahydroretene.—(a) *Incomplete dehydrogenation.* 1 G. of octahydroretene, b. p. 191—193/10 mm., and 0·3 g. of Raney nickel were similarly heated, until about 200 c.c. of gas had been evolved (corresponding to about 2 moles of hydrogen). The dehydrogenation product was dissolved in ether and separated from the catalyst by filtration.

(b) *Complete dehydrogenation.* 10 G. of octahydroretene, b. p. 191—193°/10 mm., and 3 g. of Raney nickel were similarly heated until the evolution of gas had ceased. The dehydrogenation product was separated from the catalyst by filtration when hot, and, on cooling, divided into a crystalline and an oily part. The crystals, m. p. 98—99°, were almost pure retene; the oily part was divided into two fractions of different boiling point and their infra-red spectra examined.

THE DYSON PERRINS LABORATORY AND THE
PHYSICAL CHEMISTRY LABORATORY, OXFORD.

[*Received, June 30th*, 1949.]

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53. *Vibrational Spectra of Alkyl Esters of Phosphorus Oxy-acids.*

By C. I. MEYRICK and H. W. THOMPSON.

The infra-red and Raman spectra of some alkyl esters of phosphorus oxy-acids have been measured and correlated with the molecular structure. The dialkyl hydrogen phosphites show a band which indicates a P—H bond, and implies a structure $(RO)_2HPO$ for these compounds. Characteristic frequencies for the P=O and P—O links are also suggested, and other correlations are discussed. There is reason to suppose that the P—H bond can undergo hydrogen bridge formation with neighbouring oxygen atoms.

ALTHOUGH few previous studies of the vibrational spectra of the organic derivatives of phosphorus oxy-acids have been recorded, the subject is interesting in several connexions. First, it would be useful to know whether characteristic oscillation frequencies exist for the P=O and P—O linkages, and the measurement of band intensities in the infra-red and Raman spectra might provide information about the ionic character and polarisability of these bonds. Similar measurements have recently been made for silicon–oxygen bonds (Richards and Thompson, *J.*, 1949, 124) and for related structures such as the C=O linkage (Hartwell, Richards, and Thompson, *J.*, 1948, 1436). Secondly, the increasing application of infra-red measurements to biochemical problems, both for analysis and for structural diagnosis, makes it desirable to have spectra of relevant compounds containing phosphorus for reference purposes in connexion with possible studies of phosphate metabolism and general work of this kind. Thirdly, some questions about the structure of the phosphorus oxy-acids themselves may be elucidated from the vibrational spectra.

A survey has therefore been begun of the Raman and infra-red spectra of a series of alkyl esters of phosphorus oxy-acids, and the present paper summarizes the results for several classes of compound. It will be found that useful conclusions can already be drawn with regard to some of the points indicated above.

EXPERIMENTAL METHOD.

The compounds whose spectra have been measured were synthetic products supplied by the Chemical Defence Experimental Establishment, Porton:

	n_D^{20}.	B. p.
Dimethyl hydrogen phosphite	1·4030	38°/2·5 mm.
Diethyl hydrogen phosphite	1·4080	77/17 mm.
Di*iso*propyl hydrogen phosphite	1·4080	41·5/0·5 mm.
Trimethyl phosphite	1·4088	86—86·5/351 mm.
Triethyl phosphite	1·4130	74/21 mm.
Dimethyl methylphosphonate	1·4148	79·7/20 mm.
Diethyl methylphosphonate	1·4140	56·5/3·5 mm.
Di*iso*propyl methylphosphonate	1·4109	50·5—51·5/1 mm.
Diethyl ethylphosphonate	1·4161	66—66·5/3 mm.
Di*iso*propyl ethylphosphonate	1·4151	38/0·09 mm.

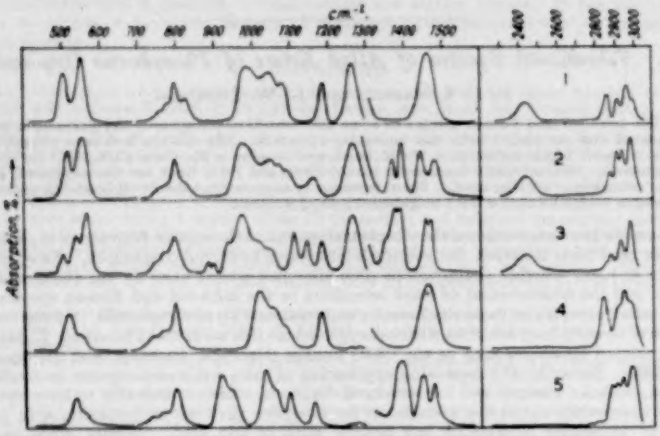
The infra-red spectra between 2 and 2·5μ. were measured with a Perkin Elmer 12 C recording spectrometer, with prisms of rock salt, potassium bromide, and lithium fluoride. Some spectra between 6 and 15μ. were also recorded on a single-beam spectrometer which has been described elsewhere (Whiffen and Thompson, *J.*, 1945, 268). Hitherto, thin films of the liquids have been used, pressed between a pair of rock salt or potassium bromide plates. Care was taken to minimise hydrolysis of the samples in damp air, and the measurements were made as rapidly as possible. As explained below, some measurements were repeated after the sample had been left in contact with damp air, and these served to indicate some of the spectral changes likely to occur in such circumstances.

The Raman spectra were measured photographically using a Hilger E518 instrument with glass prism, Ilford H.P. 3 plates being used. The exciting source was a 500-watt Hanovia cylindrical mercury arc, placed alongside a cylindrical glass tube containing a copper–ammonium salt solution. The latter acted both as a filter for the 4358a. line and as a condensing lens. The slight continuum was reduced by the introduction of further filters, a dilute solution of a rhodamine dye being sometimes used. Lines from a copper arc and neon discharge tube were used as reference standards.

Results.

The infra-red absorption spectra are shown in Figs. 1 and 2. The intensities for different compounds are not strictly comparable owing to the small differences in the thickness of the

Fig. 1.



(1) *Dimethyl hydrogen phosphite.* (2) *Diethyl hydrogen phosphite.* (3) *Diisopropyl hydrogen phosphite.* (4) *Trimethyl phosphite.* (5) *Triethyl phosphite.*

liquid used; and also different spectral regions for a given compound were measured with different thicknesses of material in order to bring up weak bands. This does not, however, affect the main conclusions of the present work. For later quantitative measurements on the intensities of the bands, it will be necessary to use known concentrations in a solvent, or alternatively known pressures of the vapours. It may be noted that the bands between 1300 and 1550 cm.$^{-1}$ are usually much weaker than many others in the spectra.

The Raman data and the position of the infra-red absorption bands are summarised in Table I and II.

Discussion.

A number of interesting deductions can be made from these results. For example, in both the infra-red and the Raman spectra, the dialkyl hydrogen phosphites show a band near 2435 cm.$^{-1}$ which is absent from the spectra of all other compounds. There can be no doubt that this is due to a stretching vibration of the P—H link, corresponding to that of Si—H bonds near 2200 cm.$^{-1}$. In phosphine there is a P—H stretching vibration frequency at 2327 cm.$^{-1}$. Now the phosphonates have formula (I), and the trialkyl phosphites (II). For the dialkyl hydrogen phosphites two possibilities arise, namely (III) and (IV), and the spectra therefore indicate (IV),

at any rate for the compounds measured. It is possible, however, that when the radicals R are changed this conclusion may not apply.

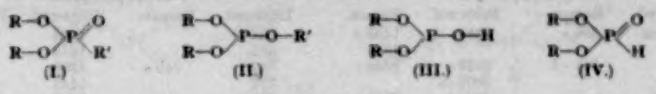
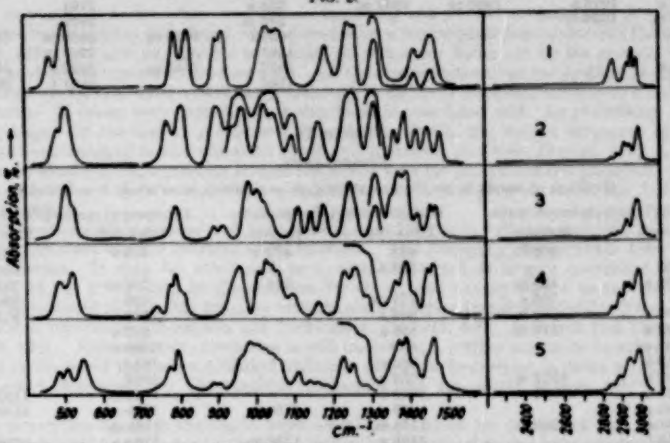


FIG. 2.



(1) *Dimethyl methylphosphonate.* (2) *Diethyl methylphosphonate.* (3) *Diisopropyl methylphosphonate.* (4) *Diethyl ethylphosphonate.* (5) *Diisopropyl ethylphosphonate.*

TABLE I.

Phosphites.

(Position of bands in cm.$^{-1}$; s = strong, m = medium, w = weak, b = broad.)

Dimethyl hydrogen phosphite.		Diethyl hydrogen phosphite.		Diisopropyl hydrogen phosphite.	
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
505 s		517 s		504	
554 s		555 s		538 m	
759	762 s		737 s	560 s	
777		760 ?			720 s
795 s		780 ?		760	765 w
825 m		795 s	802 ?	775	
985 s	990 m	822 ?		795 s	
1045 s		980 s		885	888 s
1080 m			1000 w	894	
1190 m	1199 w	1046 m		937	
1266 s	1258 m	1074		975 s	
1460	1458 s	1100	1100 m	1020	
2434 m.b.	2432 s.b.	1165		1053	
2856 m	2860 s	1261 s	1250 m	1110 m	1113 w
2922		1370		1146 m	1144
2962 s	2960 s	1392		1180 m	
2998	3010 m	1445	1445 s	1262 s	1258 m
		1480		1350 ?	1352 m
		2434 m.b.	2432 s.b.	1375	
		2851 ?		1390	
		2874		1458	1450 s
		2910 m		1468	
		2936 m	2940 s	2434 m.b.	2435 s.b.
		2981 s	2975 s	2852 ?	
				2880	2882 m
				2937 m	
				2961 s	2982 s

TABLE I (*continued*).

Trimethyl phosphite.				Triethyl phosphite.			
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
516 m	509 s	1462	1458 s	536 m		1265	1272?
552			2785	555		1275	
736	744 s.b.	2838 s	2840 s	737	740 s	1390	
775		2902 m		772		1445	1445 s
795 s		2946 s	2942 s	795 s		1478	
1014 s	1015 s	2990 m	2985 m	918 s		2764	
1060 m	1058 m			942 m		2821	
1088				1035 s	1030 m	2888 m	2874 s
1121				1061		2903 m	
1183 s				1097	1095 m	2933 s	2928 s
1265				1163		2981 s	2975 s

TABLE II.

Phosphonates.

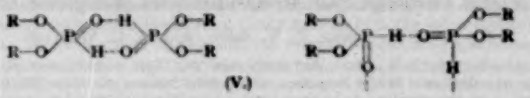
(Position of bands in cm.$^{-1}$; s = strong, m = medium, w = weak, b = broad.)

Dimethyl methylphosphonate.		Diethyl methylphosphonate.		Diisopropyl methylphosphonate.	
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
	300?	485	470 w	504 s	495 m
463		502 s			710 s
500 s	495 m		715 s	794 m	793
	706 s	771 m		898	880 m
789 s	788 m	806 s		918	915 w
822 s	816 m	895 s		983 s	
897 m		939		1008 s	
913 s		965 s		1034	
1032 s	1072 w	1023 s		1059	
1060 s	1057 w	1049 s		1112 m	1102 m
1185 m		1099 s	1100 m	1146 m	1140 w
1241 s	1240 m	1164 m		1180 m	
1256?		1250 s	1239 m	1248 s	1240 m
1315 m		1314 s		1315 m	
1419	1421 m	1365		1375	1350 m
1463	1465 m	1390		1390	
2864 s	2851 m	1420		1420	
2938 m	2929 s	1448	1445 m	1458	1445 s
2966 s	2961 w	1480		1468	
2989 s	2990 s	2863			2778 m
		2885	2880 w	2851	2835 w
		2923 m		2879	2870 m
		2943 m	2935 s	2934 m	2930 s
		2995 s	2990 s	2983 s	2985 s

Diethyl ethylphosphonate.				Diisopropyl ethylphosphonate.			
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
483 s	500 w	1254 s		485		1165	
522 s		1292	1288 m	504	502 w	1180	
	699 s	1367		545 s		1224 s	
742		1392			700 s	1251 m	
777 m		1420?		778		1286	
794 s		1448		796 s		1375	
815	811 w	1460	1460 s	887	890 m	1388	
938		1480		897		1418	
958 s		2853		959		1450	1450 s
1010	996?	2893	2895 w	986 s		1460	
1026 s		2914 m		1008		1469	
1042	1040 w	2945 m	2940 s	1023		2855	
1060		2985 s	2990 s	1042		2889	2890 w
1098	1100 m			1059		2942 m	2940 s
1165				1107	1100 m	2983 s	2985 s
1230 s	1230 w			1142			

The very broad nature of the infra-red band at 2435 cm.$^{-1}$ and the equally broad and diffuse nature of the corresponding Raman line suggest that in the liquid state this P—H bond may be associated in a bridge through oxygen atoms similar to the familar hydrogen bridge in

–O—H···O or –N—H···O– systems, in this case leading to structures such as (V). Measurements with dilute solutions are now being planned to examine this further.



(V.)

We may now consider other correlations involving the P—O—C skeleton. A previous suggestion for phosphites and phosphonates based upon a few isolated measurements (Thompson, *J.*, 1948, 328) must now be regarded as invalid, since it is not borne out by the present results and can now be interpreted in another way. All the compounds except the trialkyl phosphites have an intense band at 1250—1260 cm.$^{-1}$, although in the more complex derivatives a doubling occurs here. It seems very probable that this band is associated with the stretchings of the P=O linkage. In the case of phosphorus oxychloride, $POCl_3$, the Raman frequency of 1295 cm.$^{-1}$ has been assigned to this vibration (Yost and Anderson, *J. Chem. Physics*, 1934, **2**, 624), and there is usually a corresponding Raman frequency with the phosphites and phosphonates, as was also pointed out by Arbusov, Batuev, and Vinogradova (*Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **54**, 599).

All the compounds now measured have a band near 795 cm.$^{-1}$, with the exception of diethyl methylphosphonate where a splitting seems to occur. This frequency also occurs in some of the Raman spectra. It may be attributed to a vibration which is largely controlled by the stretching of the P—O bond in the skeleton P—O—C, and having regard to the change in reduced mass would fall roughly into line with the corresponding frequencies for C—O and Si—O bands found previously (Thompson and Torkington, *J.*, 1945, 640; Richards and Thompson, *J.*, 1949, 124). Although this correlation is still uncertain, a further argument in support of it is found in the result that when a dialkyl hydrogen phosphite hydrolyses in damp air, the band at 795 cm.$^{-1}$ disappears, as the skeleton undergoes the important change –P—O—C to –P—O—H.

The absorption bands in the region 2800—3000 cm.$^{-1}$, which are connected with stretching vibrations of C—H bonds, reveal a close parallelism between the different compounds examined. It is clear that there are frequencies typical of CH_3 and CH_2 groups which may also differ slightly according to whether they are attached to carbon or to phosphorus. The spectra of all the compounds containing two or three methoxy-groups have an infra-red band at 2840—2860 cm.$^{-1}$ lying lower than the remainder, and the location and relative intensities of the other bands between 2900 and 3000 cm.$^{-1}$ are closely parallel with the alkyl radicals concerned. It may also be noted that examination of the region 1350—1500 cm.$^{-1}$, where the deformation vibrations of alkyl groups occur, reveals similar regularities. The differences are so well marked as to be a possible means for the identification and estimation of the alkyl groups concerned.

In the other parts of the spectrum there are some regularities which suggest possible correlation rules, but with less convincing precision. The dialkyl hydrogen phosphites have a strong band near 550 cm.$^{-1}$, and in addition all the compounds have a band near 500 cm.$^{-1}$. Between 900 and 1200 cm.$^{-1}$ there will be skeleton vibrations controlled by –C—O and possibly –P—C bonds. Here too, some regularities occur according to the alkoxy-radicals concerned, but the situation is complex. In some respects the position is similar to that found in esters and alkoxysilanes. The derivatives containing *iso*propyl radicals show very similar spectra between 850 and 1050 cm.$^{-1}$.

It is evident that interesting comparisons may be made if the extinction coefficients of some of the key bands are determined. It may then be possible to correlate the ionic character of bonds such as P=O, S=O, and N=O, or P—O and C—O. These measurements are now to be carried out with vapours and solutions.

We are indebted to Dr. A. Childs for the compounds examined, and we thank the Chief Scientific Officer, Ministry of Supply, for permission to publish the results.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, July 26th*, 1949.]

54. *Researches on Acetylenic Compounds. Part XXII. The Reaction Between Nickel Carbonyl and Monosubstituted Acetylenic Compounds.*

By E. R. H. Jones, T. Y. Shen, and M. C. Whiting.

The reaction between monosubstituted acetylenes (RC≡CH), nickel carbonyl, and water in the presence of acids leads to the formation of α-substituted acrylic acids [$RC(CO_2H)=CH_2$]. The application of this reaction to various types of acetylenic alcohol has been studied; the expected substituted acrylic acids are obtained, but with αβ-acetylenic carbinols [*e.g.* $CHPr(OH)\cdot C\equiv CH$], it is preferable to employ the acetates rather than the free alcohols, and the products from βγ-acetylenic carbinols [*e.g.*, $CH_2(OH)\cdot CH_2\cdot C\equiv CH$] cyclise spontaneously to lactones. In this way the synthesis of the naturally occurring antibiotic, α-methylenebutyrolactone, has been achieved. The behaviour of certain other monosubstituted acetylenes has been examined, and some conclusions relating to the part played by water in the reaction are drawn.

Certain reports on wartime work by W. Reppe and his co-workers (B.I.O.S. Final Reports Nos. **266**, **355**, and **358**; see also *Experientia*, **1949**, **5**, **93**) contain brief descriptions of a novel reaction in which acetylenic compounds are treated either with nickel carbonyl and an acid at about 40° (" stoicheiometric process ") or with carbon monoxide under pressure at 100—180° in the presence of a nickel halide (" catalytic process "). In each case a compound possessing an active hydrogen atom, *e.g.*, water or an alcohol, is also present. The overall equations are given as :

Stoicheiometric

$$4RC\equiv CH + Ni(CO)_4 + 4EtOH + 2HCl \rightarrow 4RC(CO_2Et)=CH_2 + NiCl_2 + H_2$$

Catalytic

$$RC\equiv CH + CO + EtOH \xrightarrow[\text{halide}]{Ni} RC(CO_2Et)=CH_2$$

It is implied that when carbon monoxide and a nickel halide are used nickel carbonyl is formed *in situ* and is the effective catalyst, and that the two methods are essentially similar. Acrylic acid or its derivatives are formed from acetylene itself, and it is stated that mono- and di-substituted acetylenes give, respectively, α-substituted and αβ-disubstituted acrylic acids, unsymmetrical disubstituted acetylenes giving a mixture of the two possible products. It is claimed that alcohols, water, amines, and thiols can be used as the active-hydrogen-containing component, and that a wide variety of acetylenes may be employed; however, except in the case of acetylene itself, no experimental details are given.

The reaction between some monosubstituted acetylenes (mostly alcohols of various types), nickel carbonyl, and water in the presence of acids (" stoicheiometric process ") has been examined, partly in order to prepare some otherwise inaccessible αβ-unsaturated lactones and hydroxy-acids of possible biological interest (*cf.* Haynes, *Quarterly Reviews*, **1948**, **2**, 46) and partly in an attempt to obtain information concerning the mechanism of this reaction. Work directed towards the second end is still in progress, and the present contribution is concerned only with the preparative aspect of the reaction and with the part played in it by water. Once a moderately satisfactory technique for effecting the reaction had been evolved it was applied to a variety of compounds with little variation; the conditions employed are therefore to some extent arbitrary.

Because of the lack of information on the German work, reactions with the hydrocarbons, hex-1-yne and phenylacetylene, were first carried out. When either of these was dissolved in a mixture of ethanol and concentrated hydrochloric acid and treated with an alcoholic solution of nickel carbonyl at about 55° an exothermic reaction took place after a short induction period. The proportions of the reactants were in accordance with the equation already given except that ethanol was used in large excess as the solvent and, because of the difficulty of weighing accurately small quantities of nickel carbonyl, a moderate (10—25%) excess was always employed. Isolation of the neutral fraction at the end of the reaction gave ethyl α-butylacrylate and ethyl atropate, each in about 50% yield; in the case of phenylacetylene it was also possible to isolate a small quantity (5% yield) of atropic acid, presumably in equilibrium with the ester. None of the starting material was recoverable in either case.

When this method was applied to representative αβ-acetylenic carbinols (propylethynylcarbinol and 1-ethynylcyclohexanol) however, no exothermic reactions were observed, no appreciable yields of the expected hydroxy-esters were obtained, and in both cases considerable

amounts of the starting materials were recovered. In an endeavour to find satisfactory methods for these compounds numerous procedures were examined, including the addition of quinol or alternatively of benzoyl peroxide to the reaction mixture, and the use of the acetate in place of the carbinol itself, both under the normal conditions and (in the expectation of obtaining a mixed anhydride; cf. the German work) with the ethanol replaced by glacial acetic acid. In all these cases no exothermic reaction was observed; but when propylethynylcarbinol in *n*-propanol and acetic acid was treated with nickel carbonyl at 95° a violent reaction took place, and distillation of the neutral fraction gave some heterogeneous high-boiling material. Finally it was found that the acetate of propylethynylcarbinol (I) underwent a smooth exothermic reaction in ethanol containing acetic acid, although the induction period was rather lengthy unless a temperature of about 70° was used. Surprisingly, distillation of the neutral fraction of the reaction product gave very little volatile material, which moreover was heterogeneous. The acidic fraction on the other hand was appreciable in quantity and crystallised readily, giving the *acetoxy-acid* (II), m. p. 69°, in 40% yield.

(I.) $CHPr(OAc)\cdot C{\equiv}CH \longrightarrow CHPr(OAc)\cdot C(CO_2H){=}CH_2$ (II.)

It was concluded that in this reaction, since the free acid and not the ester was formed, water must be involved. When the requisite amount of water was added to the alcohol used the yield was improved to 48%.

This technique, *i.e.*, the use of ethanol as solvent, glacial acetic acid in slight excess, and 0·5—2 molecular equivalents of water (within these limits the amount used appeared to be immaterial) with a reaction temperature of about 70°, was now applied to a number of acetylenes. It gave satisfactory yields of the free acids (35% and 48%) with the hydrocarbons, hex-1-yne and phenylacetylene, and also with the acetates of phenylethynylcarbinol (50%) and propargyl alcohol (40%). The tertiary carbinyl acetates derived from dimethylethynylcarbinol and 1-ethynyl*cyclo*hexanol, however, still failed to react exothermally, although in the latter case isolation of the acidic fraction of the reaction mixture gave a very small yield of the expected *acetoxy-acid* (III; $R_1R_2 = [CH_2]_5$, $R_3 = Ac$), m. p. 98·5°. Rather unexpectedly propargyl alcohol reacted exothermally under these conditions, but the isolation of the product, presumably

$R_1R_2C(OR_3)\cdot C(CO_2H){=}CH_2$ (III.)

the somewhat unstable and very water-soluble hydroxy-acid (III; $R_1 = R_2 = R_3 = H$), was not possible. Phenylethynylcarbinol itself failed to react exothermally, but isolation of the acidic fraction of the reaction product gave a 10% yield of the expected *hydroxy-acid* (III; $R_1 = Ph$; $R_2 = R_3 = H$), accompanied by much syrupy, acidic material.

It therefore appears that with αβ-acetylenic carbinols and their acetates the reaction can proceed either exothermally and in good yield, or slowly without visible evolution of heat and in poor yield. The first type of reaction is observed with propargyl acetate and probably propargyl alcohol, and with secondary carbinyl acetates; the second with free secondary carbinols, tertiary carbinols, and tertiary carbinyl acetates.

The products thus obtained from the α-carbinols and their acetates showed the expected properties (hydrolysis and alcoholysis of the acetyl groups, esterification, etc.). Perhaps the most interesting was the compound (III; $R_1 = R_2 = H$; $R_3 = Ac$), m. p. 53°, prepared from propargyl acetate. This was hydrolysed with barium hydroxide solution to the corresponding *hydroxy-acid* which showed a strong tendency to polymerise, *e.g.*, during an attempted isolation by continuous extraction of an aqueous solution with ether. The polymer proved to be insoluble in methanol and acetone but readily soluble in water. Its *methyl* ester, prepared by treating the acetoxy-acid with methanolic sulphuric acid, is closely related to methyl methacrylate. Like the hydroxy- and acetoxy-acids it was found to be much less stable than analogues derived from secondary acetylenic carbinols.

When the method first used, *i.e.*, ethanol–hydrochloric acid at 55°, was applied to the βγ-acetylenic carbinols, but-3-yn-1-ol and pent-4-yn-2-ol (IV; R = H and Me), an exothermic reaction took place in both cases, and distillation of the neutral fractions of the reaction mixtures

(IV.) $RCH(OH)\cdot CH_2\cdot C{\equiv}CH \longrightarrow RCH\cdot CH_2\cdot C{=}CH_2$ (V.)
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O\text{——}CO$

gave the two α-methylene-γ-lactones (V; R = H and Me, respectively) as liquids which polymerised on storage to clear glasses.[6] Some polymerisation seemed to take place during the reaction, and it was suspected that the products were somewhat impure. When the aqueous-ethanolic acetic acid technique was employed in these two cases no polymer was formed, and

the two lactones obtained (yields 23% and 30%, respectively) proved to be homogeneous; the refractive indices differed slightly from those of specimens obtained by the hydrochloric acid method. They could be kept at room temperature for several weeks, or indefinitely when quinol was added. It is noteworthy that (V; R = H; "α-methylenebutyrolactone") was obtained by Cavallito and Haskell (*J. Amer. Chem. Soc.*, 1946, **68**, 2332) by the hydrolysis of a presumably glycosidic precursor occurring in *Erythronium americanum*, and was found by them to exhibit weak antibacterial properties. More complex substances containing the α-methylenebutyrolactone grouping have been isolated from natural sources [Asahina and Asano, *J. Pharm. Soc. Japan*, 1927, **539**, 1 (*Chem. Abstracts*, 1928, **22**, 4470); Asano and Kanematsu, *Ber.*, 1932, **65**, 1174; Cavallito and Kirchner, *J. Amer. Chem. Soc.*, 1947, **69**, 3030], but no previous synthesis of this type of compound has been reported. The physical properties of the synthetic material agreed well with those recorded by Cavallito and Haskell (*loc. cit.*), but the synthetic lactone did not show the skin-irritant properties of the natural product. It is possible that the latter contained a trace of some other substance which was responsible for these, or that individual susceptibility varies widely.

On being heated to 100° in the presence of a little benzoyl peroxide the two lactones polymerised to clear, hard resins, softening at 160—190°.*

Attempts were made to improve the yield of α-methylenebutyrolactone by carrying out the nickel carbonyl reaction with the *acetate* of but-3-yn-1-ol, whereby the *acid* $AcO{\cdot}CH_2{\cdot}CH_2{\cdot}C(CO_2H){=}CH_2$ (p-*bromophenacyl* ester, m. p. 76°) was readily obtained in 47% yield. Attempts to hydrolyse this with alkali or to effect cyclisation to (V; R = H) by treatment with 1% methanolic sulphuric acid proved relatively unsuccessful since only moderate (30—60%) yields of rather impure lactone were obtained, apparently because of the instability of the latter towards mineral acids. This factor was probably responsible for the poor quality of the material obtained from but-3-yn-1-ol and nickel carbonyl when hydrochloric acid was used. As a further variant the hydroxyl group of but-3-yn-1-ol was protected by reaction with 2 : 3-dihydropyran (cf. Woods and Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246); the expected *ether* was readily obtained, but its reaction with nickel carbonyl gave only a 20% yield of the corresponding *acid*, the conversion of which into the methylenelactone (V) was therefore not studied.

In view of the differences between the primary, secondary, and tertiary types of αβ-acetylenic carbinols it was of interest to examine the behaviour of the tertiary βγ-acetylenic carbinol, 2-methylpent-4-yn-2-ol (Henbest, Jones, and Walls, *J.*, 1949, 2696). No exothermic reaction was observed, but after careful fractionation a 10% yield of the expected *lactone* (VI) was obtained. Its behaviour is thus similar to that of the secondary αβ-carbinol, phenylethynylcarbinol. The reaction with nickel carbonyl of the only γδ-acetylenic carbinol so far reported, pent-4-yn-1-ol (Lespieau, *Compt. rend.*, 1932, **194**, 287; Eglinton, Jones, and Whiting, forthcoming publication) was also examined. With this compound an exothermic reaction was observed, and the δ-lactone (VII) was obtained in 20% yield.

(VI.) $Me_2C{\cdot}CH_2{\cdot}C{=}CH_2$ (lactone ring: O—CO) (VII.) $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C{=}CH_2$ (lactone ring: O—CO)

Concurrently with the work on acetylenic carbinols the application of the nickel carbonyl reaction to monosubstituted acetylenes of some other types was attempted. With the vinylacetylenic compounds, 2-methylpent-1-en-3-yne, 1-ethynylcyclohexene, pent-2-en-4-yn-1-ol, and pent-2-en-4-yn-1-yl acetate no exothermic reactions were observed either in ethanolic hydrochloric acid or in aqueous–ethanolic acetic acid. In the case of 1-ethynylcyclohexene under the latter conditions, isolation of the acidic fraction gave only a 1·5% yield of a high-melting solid clearly not the expected acid. No exothermic reaction was observed with phenyl ethynyl ketone (acetic acid technique); as was the case with the reactions involving vinylacetylenes, much dark polymeric material was formed.

In this communication the results of investigations, as yet incomplete, with various disubstituted acetylenes, and on the mechanism of the reaction, will not be discussed. However, even at this stage it can be pointed out that it is almost certainly the free acids, and not the esters, which are formed initially in this reaction, and the presence of water (either added to the reaction mixture or formed *in situ* in side reactions) is necessary. This is convincingly demonstrated by the fact that even when carefully dried ethanol is employed as solvent in experiments employing acetic acid, the free acid and not the ester is the principal product. In

* Patents applied for (B.P. Applications, 7091 and 7092/48).

most reactions a little ester is also formed (its isolation is usually difficult and was not generally attempted) but this is in all probability the result of subsequent esterification, which of course takes place to equilibrium when a mineral-acid catalyst is present. When dried alcohol was used as solvent the yields of crystalline acids in the cases of phenylacetylene and phenylethynylcarbinyl acetate were reduced to 30% and 24%, respectively (normally 48% and 50%). If it is assumed that the hydrogen formed in the reaction according to the equation given by Reppe is converted into water a 25% yield of the acid would be possible.*

The light-absorption properties of the acids and lactones obtained are shown below.

Compound.	λ, A.	ε.	Compound.	λ, A.	ε.
$CH_2(OH)\cdot C(CO_2H)=CH_2$	2140	3000	$CH_2\cdot CH_2\cdot C(=CH_2)\cdot O\cdot CO$ (in water)	2200 [1]	7500
	2300	300		2250	5000
				2350	900
$CHPr(OH)\cdot C(CO_2H)=CH_2$	2150	6500		2400	400
	2450	1300		2450	250
$CHPh(OH)\cdot C(CO_2H)=CH_2$	2170	7000	$CH_2\cdot CH_2\cdot C(=CH_2)\cdot O\cdot CO$ (in water) [2]	2300	2400
	2380	1800		2350	900
				2400	500
$[CH_2]_5>C(OH)\cdot C(CO_2H)=CH_2$	2190	4000			
	2250	1200	$CH_2\cdot CH_2\cdot CH_2\cdot C(=CH_2)\cdot O\cdot CO$ (in water)	2200 [1]	5700
				2250	4450
$[CH_2]_5>C(OAc)\cdot C(CO_2H)=CH_2$	2170	4000		2300	3100
	2320	900		2350	1750
				2400	1000
$CH_2\cdot CH_2\cdot C(=CH_2)\cdot O\cdot CO$	2200	5000		2450	470
	2250	500			

None of the above compounds exhibited any maximal absorption in the range examined.

Except where otherwise stated alcoholic solutions were employed and a Hilger Medium Spectrograph was used.

[1] Beckman spectrograph used. [2] Cavallito and Haskell, *loc. cit.*

Experimental.

General Method.—The apparatus consisted of a flask of 250 c.c. capacity equipped with a thermometer whose bulb dipped into the liquid in the flask, a mercury-seal stirrer, a reflux condenser, a gas inlet, and a dropping funnel. The acetylenic compound, the solvent, the acid used, and in some cases water were stirred under nitrogen while the flask was heated with a free flame until the liquid reached the desired temperature (55—60°). About 2 c.c. of the solution of nickel carbonyl were added and, after an induction period of variable length, the reaction began, as shown by a marked rise in temperature and in some cases a transient deep-brown coloration. The remainder of the carbonyl solution was then added dropwise at such a rate that the temperature remained constant until the reaction was complete, when the temperature began to fall. As soon as the reaction mixture was sufficiently cool, ether (5—10 times the volume of nickel carbonyl used) was added, the apparatus was adapted for distillation, and the flask was warmed on the steam-bath until everything volatile under these conditions had distilled. The distillate was poured away carefully.

Up to this stage all operations were carried out in a well-ventilated fume-cupboard, but when the excess of nickel carbonyl had been removed the reaction mixture could be handled in the open laboratory. The solution was poured into dilute sulphuric acid and extracted with ether or chloroform; the extract was washed thoroughly with sodium hydrogen carbonate solution, and the neutral and acidic fractions were isolated, the procedure varying from case to case.

Ethyl Atropate.—The reaction was carried out by the general method, using phenylacetylene (20·6 g.), ethanol (60 c.c.), and concentrated hydrochloric acid (8 c.c.), to which a solution of nickel carbonyl (6·6 c.c.) in ethanol (20 c.c.) was added. The temperature was kept at 55° by occasional external cooling. The acid fraction gave, after crystallisation from water, atropic acid (1·5 g.), m. p. 105—106°; the neutral portion was distilled giving the ester (16·7 g.), b. p. 57—63°/10^{-3} mm., n_D^{25} 1·5229 (Auwers and Eisenlohr, *J. pr. Chem.*, 1911, **84**, 89, give b. p. 120·2—120·4°/14 mm., n_D^{18} 1·5260).

Ethyl α-Butylacrylate.—Hex-1-yne (16·4 g.), ethanol (60 c.c.), and concentrated hydrochloric acid (9 c.c.) reacted at 50—70° with a solution of nickel carbonyl (8 c.c.) in ethanol (20 c.c.). Isolation with pentane gave ethyl α-butylacrylate (16·0 g.), b. p. 66°/10 mm., n_D^{25} 1·4290 (Blaise and Luttringer, *Bull. Soc. chim.*, 1905, **33**, 778, give b. p. 177°).

Atropic Acid.—(a) The reaction was carried out by the general method at 70° using phenylacetylene (15·3 g.), acetic acid (6 c.c.), ethanol (30 c.c.), water (2 c.c.), and a solution of nickel carbonyl (6 c.c.) in ethanol (15 c.c.). Isolation of the acidic fraction followed by crystallisation from light petroleum (b. p. 60—80°) gave atropic acid (10·65 g., 48%) as prismatic needles, m. p. 106—107° (Fittig and Wurster, *Annalen*, 1879, **196**, 147, give m. p. 106—107°). From the mother-liquors a solid (380 mg.), m. p. 89—90°,

* Since writing the above account it has been found that an exothermic reaction takes place on adding nickel carbonyl to a solution of phenylacetylene and glacial acetic acid in dry anisole at 60°, atropic acid being obtained in 20% yield. In this case the water required must clearly be formed in side-reactions involving nickel carbonyl and the acetylene, since none could be formed from the solvent mixture alone.

was obtained by crystallisation. Recrystallisation of this from light petroleum (b. p. 60—80°) gave irregular rhombic plates, m. p. 86—87° undepressed on admixture with atropic acid (mixed m. p. 90—94°) (Found: C, 73·65, 71·75; H, 5·45, 5·4%). Light absorption: Maxima at 2900 and 2800 A., $E^{1\%}_{1\,cm.}$ = 430 and 330, respectively (cf. atropic acid, which has a maximum at 2560 A., $E^{1\%}_{1\,cm.}$ = 350, and end absorption). The constitution of this solid was not investigated further.

(*b*) Repetition of this experiment using ethanol dried over magnesium ethoxide, and omitting the water gave crude atropic acid, m. p. 101—103° (6·65 g.). Crystallisation of this material gave the pure acid, m. p. 106—107° (5·6 g., 30%).

α-Butylacrylic Acid.—Hex-1-yne (41 g.), ethanol (100 c.c.), glacial acetic acid (15 c.c.), and water (7 c.c.), reacted with a solution of nickel carbonyl (17 c.c.) in ethanol (50 c.c.) at *ca.* 67° by the general method in a 1-l. flask. Isolation of the acidic fraction followed by distillation gave α-butylacrylic acid (21·75 g.), b. p. 69—70°/0·2 mm., n_D^{25} 1·4453 (Blaise and Luttringer, *loc. cit.*, give b. p. 109—110°/10 mm.).

3-Acetoxyhex-1-ene-2-carboxylic Acid (II).—Propylethynylcarbinyl acetate (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 45) (9·3 g.), ethanol (20 c.c.), glacial acetic acid (5 c.c.), and water (1 c.c.) reacted at 74—78° by the general method with nickel carbonyl (3 c.c.) in ethanol (10 c.c.). Isolation of the acidic fraction with chloroform, followed by evaporation of the solvent, gave a residue which solidified when scratched and, on crystallisation from light petroleum (b. p. 40—60°), gave a product (5·9 g., 48%), m. p. 67°. Recrystallisation from the same solvent gave the *acetoxy-acid* as long needles, m. p. 68·5° (Found: C, 58·2; H, 7·6. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%).

3-Hydroxyhex-1-ene-2-carboxylic Acid (III; $R_1 = R_2 = H$, $R_3 = Pr$).—The acetoxy-acid (3 g.) was dissolved in a solution of potassium hydroxide (3 g.) in water (6 c.c.) with cooling. After 18 hours at 20° the solution was acidified; isolation with ether followed by distillation at 80° (bath temp.)/10^{-4} mm. gave the *hydroxy-acid* (1·65 g.) as a syrup, n_D^{25} 1·4685 (Found: C, 58·35; H, 8·75. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%). The *ethyl* ester was prepared by heating the hydroxy-acid (2·5 g.), ethanol (12 c.c.), and concentrated sulphuric acid (0·6 c.c.) under reflux for three hours. Isolation of the product with ether and distillation gave the ester (2·3 g.), b. p. 95°/5·5 mm., n_D^{25} 1·4521 (Found: C, 62·75; H, 9·6. $C_9H_{16}O_3$ requires C, 62·75; H, 9·35%). The ethyl ester *α-naphthylurethane*, prepared at room temperature, formed felted needles, m. p. 88°, from light petroleum (b. p. 60—80°) (Found: N, 4·1. $C_{20}H_{23}O_4N$ requires N, 3·95%).

3-Acetoxy-3-phenylprop-1-ene-2-carboxylic Acid (III; $R_1 = H$, $R_2 = Ph$, $R_3 = Ac$).—Phenylethynylcarbinyl acetate (Jones and McCombie, *J.*, 1942, 733) (11·6 g.), ethanol (20 c.c.), glacial acetic acid (3 c.c.), and water (2 c.c.) reacted at 70° by the general method with nickel carbonyl (3 c.c.) in ethanol (10 c.c.). Isolation of the acidic fraction with ether gave an oil which soon solidified; crystallisation from light petroleum (b. p. 60—80°) gave the *acetoxy-acid* (7·4 g., 50%) as stout needles, m. p. 110·5° unchanged on recrystallisation from the same solvent (Found: C, 65·45; H, 5·5. $C_{13}H_{12}O_4$ requires C, 65·25; H, 5·55%).

3-Hydroxy-3-phenylprop-1-ene-2-carboxylic Acid (III; $R_1 = R_2 = H$, $R_3 = Ph$).—(*a*) The acetoxy-acid (3 g.) was dissolved in a solution of sodium hydroxide (2 g.) in water (20 c.c.). After storage at 20° for 48 hours, acidification and isolation with ether gave a syrup which was induced to crystallise by keeping it for several hours at 35°. Recrystallisation from benzene gave a product (2·0 g.), m. p. 79—80°; after further recrystallisation from the same solvent the *hydroxy-acid* formed fine needles, m. p. 81° (Found: C, 67·15; H, 5·35. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·65%).

(*b*) Phenylethynylcarbinol (18·3 g.), ethanol (30 c.c.), glacial acetic acid (6 c.c.), and water (2 c.c.) were heated to 80° and maintained at about this temperature while a solution of nickel carbonyl (6 c.c.) in ethanol (15 c.c.) was added in small portions during 20 minutes. No exothermic reaction took place; isolation of the acidic fraction with ether gave a syrup (7·0 g.) whose benzene solution, on addition of light petroleum (b. p. 60—80°) and seeding with material obtained by method (*a*), gave the crude hydroxy-acid (3·1 g.), m. p. 72—75°. After recrystallisation from benzene this had m. p. 81°, undepressed on admixture with a specimen prepared by method (*a*).

3-Acetoxyprop-1-ene-2-carboxylic Acid (III; $R_1 = R_3 = H$, $R_2 = Ac$).—Propargyl acetate (6·5 g.), ethanol (20 c.c.), glacial acetic acid (3 c.c.), and water (1 c.c.) were heated to 70°, and a solution of nickel carbonyl (3 c.c.) in ethanol (10 c.c.) was added, the temperature being maintained at about 75°. After removal of the excess of nickel carbonyl, ether (100 c.c.) was added, and the solution was shaken with a solution of concentrated sulphuric acid (1 c.c.) in water (10 c.c.), which was then extracted with ether (2 × 20 c.c.). The combined ethereal extracts were shaken with a slight excess of a saturated solution of potassium hydrogen carbonate, which was acidified with concentrated hydrochloric acid. After being decanted from the precipitate of potassium chloride, which was washed well with ether, the aqueous solution was extracted with ether (5 × 150 c.c.). Evaporation of most of the solvent from the dried extract through an 8-inch Lapworth column and the removal of the remainder under reduced pressure below 20° gave an oil which readily solidified; crystallisation from light petroleum (b. p. 40—60°) contaning a little benzene gave a product (3·1 g.), m. p. 49—50°; a further 0·6 g. of less pure material, m. p. 44°, was obtained from the filtrate. After recrystallisation from light petroleum (b. p. 40—60°) the *acetoxy-acid* formed nacreous leaflets, m. p. 53° (Found: C, 50·2; H, 5·8. $C_6H_8O_4$ requires C, 50·0; H, 5·6%).

3-Hydroxyprop-1-ene-2-carboxylic Acid (III; $R_1 = R_2 = R_3 = H$).—The acetoxy-acid (2·05 g.) was dissolved in a solution of barium hydroxide (4 g.) in water (40 c.c.). After 24 hours the solution was brought to pH *ca.* 2·5 by adding sulphuric acid; after filtration it was found to give no precipitate with barium chloride solution and only a very faint turbidity with sulphuric acid. Evaporation under reduced pressure and distillation at 60—75° (bath temp.)/10^{-4} mm. gave the *hydroxy-acid* (530 mg.), n_D^{25} 1·4760 (Found: C, 46·4; H, 6·4. $C_4H_6O_3$ requires C, 47·05; H, 5·95%).

Methyl 3-Hydroxyprop-1-ene-2-carboxylate.—The acetoxy-acid (2·5 g.), methanol (15 c.c.), and concentrated sulphuric acid (0·5 c.c.) were heated under reflux for five hours. Ether (25 c.c.) was added and the solution was washed with a solution of potassium carbonate (1·5 g.) in water (2 c.c.), the aqueous

layer being extracted with ether (2 × 5 c.c.). The combined extracts were partly dried (Na_2SO_4), and the ether and methanol were evaporated off through an 8-inch Lapworth column. The residue contained a large quantity of water; chloroform and sodium sulphate were added, and, after some time, the latter was separated and the chloroform was distilled off through a column. Distillation of the residue gave the *methyl* ester, b. p. 81°/9 mm., n_D^{18} 1·4548 (Found: C, 51·6; H, 6·85. $C_9H_{14}O_3$ requires C, 52·2; H, 6·8%).

α-1-*Acetoxycyclohexylacrylic Acid* (III; $R_1R_2 = (CH_2)_5$, R = Ac).—1-Ethynylcyclohexyl acetate (Rupe, Messmer, and Kambli, *Helv. Chim. Acta*, 1928, **11**, 453) (11·1 g.), dry ethanol (20 c.c.), and glacial acetic acid (3 c.c.) were heated to 75° and maintained at about that temperature for 15 minutes while a solution of nickel carbonyl (3 c.c.) in ethanol (10 c.c.) was added in small portions. Isolation of the acidic portion of the resulting mixture with ether gave a syrup which was dissolved in light petroleum and cooled to 0°. On storage, a rather gummy solid (700 mg.) was obtained, which by crystallisation from light petroleum (b. p. 60—80°) gave the *acetoxy-acid* as stout prismatic needles (500 mg.), m. p. 98·5° unchanged on recrystallisation from the same solvent (Found: C, 62·3; H, 7·6. $C_{11}H_{16}O_4$ requires C, 62·25; H, 7·6%).

α-1-*Hydroxycyclohexylacrylic Acid* (III; $R_1R_2 = (CH_2)_5$, R = H).—α-1-Acetoxycyclohexylacrylic acid (200 mg.) was dissolved in a solution of potassium hydroxide (300 mg.) in water (1 c.c.). After 18 hours, isolation of the acidic fraction with ether gave an oil which crystallised after about two weeks at 20°. Recrystallisation from light petroleum (b. p. 60—80°), in which it was rather soluble, gave the *hydroxy-acid* (85 mg.) as acicular prisms, m. p. 78—81°. Further recrystallisation from the same solvent or from aqueous methanol did not alter the melting point; and more drastic conditions of hydrolysis did not improve the yield (Found: C, 63·85; H, 8·05. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2%).

But-3-yn-1-yl Acetate.—Acetylation of but-3-yn-1-ol (IV; R = H) (46 g.) with acetic anhydride (69 c.c.) and pyridine (55 c.c.) with cooling, then for 20 hours at room temperature, gave the *acetate* (54·5 g., 73%), b. p. 65°/40 mm., n_D^{18} 1·4230 (Found: C, 64·0; H, 7·2. $C_6H_8O_2$ requires C, 64·25; H, 7·2%).

4-Acetoxybut-1-ene-2-carboxylic Acid.—But-3-yn-1-yl acetate (7·5 g.), ethanol (20 c.c.), water (0·6 c.c.), and glacial acetic acid (3 c.c.) reacted by the general method with a solution of nickel carbonyl (3 c.c.) in ethanol (20 c.c.). Isolation of the acidic fraction with ether gave a pale yellow oil (4·1 g.), n_D^{18} 1·4520, which was distilled to give the *acid acetate* (3·4 g.), b. p. 100°/0·05 mm., n_D^{18} 1·4515 (Found: C, 53·1; H, 6·65. $C_7H_{10}O_4$ requires C, 53·1; H, 6·35%). The *p-bromophenacyl* ester separated from aqueous methanol in flat needles, m. p. 76° (Found: C, 50·75; H, 4·4. $C_{15}H_{15}O_5Br$ requires C, 50·7; H, 4·25%).

4-(2-Tetrahydropyranyloxy)but-1-yne.—To a mixture of but-3-yn-1-ol (IV; R = H) (15·0 g.) and 2 : 3-dihydropyran (18·5 g.), concentrated hydrochloric acid (0·2 g.) was added. An exothermic reaction took place which was moderated by ice-cooling. After the solution had been kept for 18 hours at 20° potassium hydroxide (0·3 g.) was added, and the precipitated potassium chloride was filtered off; distillation then gave the *ether* (26 g.), b. p. 92—95°/18 mm., n_D^{18} 1·4589 (Found: C, 70·3; H, 9·65. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%).

4-(2-Tetrahydropyranyloxy)but-1-ene-2-carboxylic Acid and its Ethyl Ester.—The above ether (11·4 g.) in ethanol (25 c.c.), glacial acetic acid (4 c.c.), and water (1·5 c.c.) reacted with a solution of nickel carbonyl (4 c.c.) in ethanol (10 c.c.) at 75°. The standard procedure was employed, an exothermic reaction taking place. Isolation of the acidic fraction then gave an oil (3·5 g.) of which a portion (2·2 g.) was distilled at 75° (bath temp.)/10^{-4} mm. to give the *acid* (1·8 g.), n_D^{18} 1·4773 (Found: C, 60·1; H, 8·05. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%). The neutral fraction was distilled to give the corresponding *ethyl* ester (1·5 g.), b. p. 82·5°/0·2 mm., n_D^{18} 1·4612 (Found: C, 63·2; H, 8·85. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·85%). Attempts to characterise the acid by preparation of crystalline *p*-nitrobenzyl and *p*-bromophenacyl esters proved unsuccessful.

4-Hydroxybut-1-ene-2-carboxylic Acid Lactone ("*α-Methylenebutyrolactone*") (V; R = H).—(*a*) But-3-yn-1-ol (IV; R = H) (10·5 g.), ethanol (30 c.c.), glacial acetic acid (6 c.c.), and water (2 c.c.) reacted at 80° with a solution of nickel carbonyl (6 c.c.) in ethanol (10 c.c.). The reaction began only after a lengthy induction period. After the excess of nickel carbonyl had been removed water was added, the solution was thoroughly extracted with ether, and the extract was washed with the minimum quantities of dilute sulphuric acid and sodium hydrogen carbonate solution. A little quinol was added at this stage. Evaporation of the solvent through an 8-inch Dufton column and distillation gave the lactone (3·4 g., 23%), b. p. 38°/0·2 mm., n_D^{18} 1·4707. Careful re-fractionation gave five fractions whose refractive indices were constant to within 0·0004 (Found: C, 60·9; H, 6·55. Calc. for $C_5H_6O_2$: C, 61·2; H, 6·15%) (Cavallito and Haskell, *loc. cit.*, give b. p. 57—60°/2 mm., n_D^{20} 1·470).

(*b*) A solution of nickel carbonyl (7 c.c.) in methanol (15 c.c.) was added to but-3-yn-1-ol (10·5 g.) in methanol (40 c.c.) and concentrated hydrochloric acid (6 c.c.) at 60°. An exothermic reaction took place; isolation of the neutral fraction (care being taken to remove powdery polymer by decantation) followed by distillation gave the lactone (3 g.), b. p. 92—95°/13 mm., n_D^{18} 1·4662. After a few days an elastic polymer was formed.

4-Hydroxypent-1-ene-2-carboxylic Acid Lactone (V; R = Me).—(*a*) Pent-4-yn-2-ol (IV; R = Me) (12·6 g.) reacted at 80° exactly as in the previous preparation [method (*a*)]. Distillation of the crude product gave the *lactone* (5·05 g.), b. p. 33°/0·02 mm., n_D^{18} 1·4596. Careful re-fractionation gave five fractions whose refractive indices were constant to within 0·0010 (Found: C, 64·5; H, 7·5. $C_6H_8O_2$ requires C, 64·25; H, 7·2%).

(*b*) The reaction was carried out by the general method at 50—55° using pent-4-yn-2-ol (12·6 g.) in methanol (45 c.c.) and concentrated hydrochloric acid (6 c.c.) and adding a solution of nickel carbonyl (5 c.c.) in methanol (15 c.c.). The reaction was strongly exothermic; isolation of the neutral fraction followed by distillation gave the lactone (7·1 g.), b. p. 87—90°/9 mm., which polymerised on storage.

4-Hydroxy-4-methylpent-1-ene-2-carboxylic Acid Lactone (VI).—2-Methylpent-4-yn-2-ol (Henbest, Jones, and Walls, *J.*, 1949, 2696) (15·8 g.) was dissolved in ethanol (30 c.c.), glacial acetic acid (7 c.c.), and water (3 c.c.), and the mixture was heated to 75—80° for 20 minutes during the addition of a solution of nickel carbonyl (8 c.c.) in ethanol (10 c.c.). No exothermic reaction was observed; isolation of the neutral fraction and distillation gave a product (3 g.), b. p. 40—64°/1·0 mm., n_D^{18} 1·4375—1·4541, which

after careful refractionation gave the *lactone* (1·5 g.), b. p. 45°/1 mm., n_D^{25} 1·4561 (Found: C, 66·5; H, 8·0. $C_5H_8O_2$ requires C, 66·6; H, 8·0%).

5-Hydroxypent-1-ene-2-carboxylic Acid Lactone (VII). Pent-4-yn-1-ol (Eglinton, Jones, and Whiting, forthcoming publication) (12·6 g.) was dissolved in ethanol (20 c.c.), glacial acetic acid (6 c.c.), and water (2 c.c.), and the mixture was heated to 80°. A solution of nickel carbonyl (6 c.c.) in ethanol (10 c.c.) was added; an exothermic reaction began only after a long induction period. Isolation of the neutral fraction and careful fractional distillation gave the *lactone* (3·5 g.), b. p. 56·5°/0·07 mm., n_D^{25} 1·4810. This appeared to be homogeneous, but despite purification by repeated fractional distillation analytical results were inaccurate (Found: C, 63·25, 63·2; H, 7·55, 7·5. $C_5H_6O_2$ requires C, 64·25; H, 7·2%). Its light-absorption properties (see table) were normal.

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55. *Researches on Acetylenic Compounds. Part XXIII. The Preparation and Properties of αβ-Acetylenic γ-Keto-esters.*

By E. R. H. JONES, T. Y. SHEN, and M. C. WHITING.

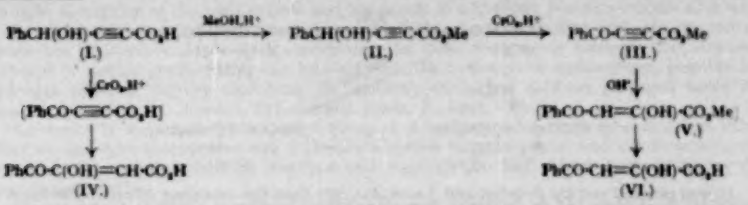
Oxidation of the esters of αβ-acetylenic γ-hydroxy-acids with chromic acid in acetone gives the γ-keto-esters. On the other hand, oxidation of the free acids is accompanied by hydration of the triple bond resulting in the formation of βγ-diketo-acids; alkaline hydrolysis of a typical γ-keto-ester leads to hydration in the opposite direction, an αγ-diketo-acid being formed. With various types of amines, the keto-esters give adducts, convertible by mild acid hydrolysis into αγ-diketo-acid derivatives, and with hydrazine, hydroxylamine, and diazomethane the keto-esters yield the expected heterocyclic compounds.

As an extension of recent work on the synthesis of acetylenic hydroxy-acids (Haynes and Jones, *J.*, 1946, 503) and on the conversion of ethynylcarbinols into the corresponding ketones (Bowden, Heilbron, Jones, and Weedon, *J.*, 1945, 39), the application of the chromic acid–acetone-oxidation procedure to the hydroxy-acids and their esters has been investigated. No general synthesis of the expected acetylenic keto-esters has been described, although Nineham and Raphael (*J.*, 1949, 118) have prepared methyl β-benzoylpropiolate (see also Ingold, *J.*, 1925, 1199) and a vinylacetylenic keto-acid has been obtained by Heilbron, Jones, and Sondheimer (*J.*, 1949, 604) by oxidation of the corresponding primary-secondary glycol.

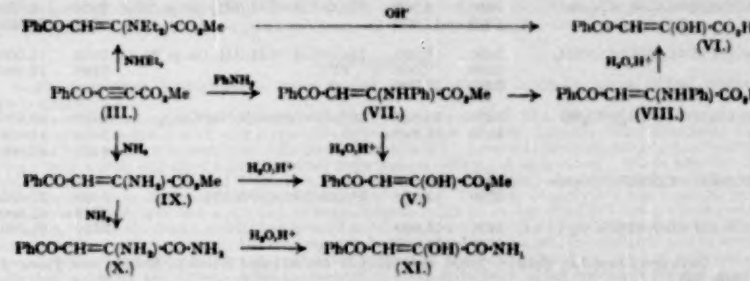
It was found that the method of Bowden, Heilbron, Jones, and Weedon (*loc. cit.*) was applicable generally to αβ-acetylenic hydroxy-esters, and *acylpropiolic esters*, RCO·C≡C·CO_2Me, have been prepared in the cases where R = Ph, Me, and Pr. They are pungent, somewhat lachrymatory, compounds which decompose readily on heating to 70—120°, and they resinify on treatment with pyridine. Their structures were confirmed by hydrogenation to known β-acylpropionic esters. Similarly, oxidation of the methyl ester of 5-hydroxyhex-3-en-1-yne-1-carboxylic acid gave the corresponding *keto*-ester (MeCO·CH=CH·C≡C·CO_2Me) as a very unstable liquid. When the same method was applied to the acetylenic hydroxy-acids themselves, however, oxidation was accompanied by hydration of the triple bond. Thus the hydroxy-acid (I) derived from phenylethynylcarbinol gave, in 40% yield, a crystalline acid which, in view of its analysis, light-absorption properties, ferric chloride coloration, and reaction with *o*-phenylenediamine to give a *quinoxaline* derivative, must be formulated as β-*hydroxy*-β-*benzoylacrylic acid* (IV) [cf. the hydration of phenyl ethynyl ketone to 1-phenylbutane-2 : 3-dione (Bowden, Braude, and Jones, *J.*, 1946, 945), which, however, requires mercuric sulphate catalysis]. The oxidation of 3-hydroxybut-1-yne-1-carboxylic acid also apparently proceeds with concomitant hydration since the unstable acidic product gave a strong ferric chloride coloration and yielded a *quinoxaline* derivative with *o*-phenylenediamine.

An obvious alternative route to the free αβ-acetylenic γ-keto-acids was by the hydrolysis of the corresponding esters. An exothermic reaction occurred on treatment of the ester (III) with aqueous methanolic potassium hydroxide and, after 24 hours α-hydroxy-β-benzoylacrylic acid (VI) (benzoylpyruvic acid) was isolated on acidification. Variable results were obtained on repetition of this alkaline hydrolysis, probably owing to the instability of the acid (VI). The

ester (V) was presumed to be an intermediate in this reaction but attempts to isolate it were unsuccessful.



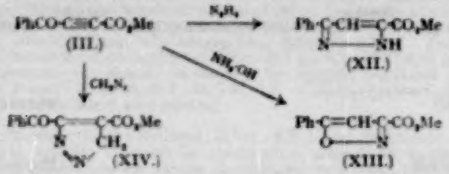
The keto-esters studied were found to react readily with amines (cf. Bowden, Braude, Jones, and Weedon, *J.*, 1945, 45). Thus methyl β-benzoylpropiolate (III), when treated with aniline, gave the crystalline *adduct* (VII) in 85% yield; the latter was hydrolysed to (V) with dilute mineral acids at room temperature, and hence has the structure shown, rather than that in which the anilino-group is in the β-position to the carbomethoxyl group. Alkaline hydrolysis gave the known acid (VIII), convertible into (VI). Treatment of methyl β-benzoylpropiolate with diethylamine gave an analogous liquid *adduct*. The reaction with ammonia was more complex; liquid ammonia caused resinification, but treatment of (III) in methanolic solution with aqueous ammonia resulted in an immediate exothermic reaction. Isolation of the product after some time gave the crystalline *amino-amide* (X) in 50% yield. When, however, the product was isolated by rapid removal of the ammonia and solvent immediately after the exothermic reaction had ceased, the *amino*-ester (IX), was obtained as a yellow oil which, after distillation at 70° (bath temp.)/10^{-4} mm., crystallised and then melted at 40°. Mild acid hydrolysis of (IX) and (X) proceeded as expected, the known enols (V) and (XI) being formed; the position of the amino-group was thus established.



The addition of ammonia to β-benzoylacrylic acid has recently been stated (Bougault and Chabrier, *Compt. rend.*, 1948, **226**, 1378), to give β-amino-β-benzoylpropionic acid, although no evidence was quoted in support of the structure assigned to the adduct. Such a result is surprising in view of an earlier discussion (Bougault, *Ann. Chim.*, 1908, **15**, 491) of the addition of nucleophilic reagents to this acid in which, by analogy with other reactions giving known α-substituted β-benzoylpropionic acids, it was considered probable that the adduct obtained from ammonia was α-amino-β-benzoylpropionic acid. Since it seems unlikely that addition of ammonia to corresponding ethylenic and acetylenic substances takes place in opposite directions, and the structure of the adduct from the latter has been unambiguously proved, the earlier interpretation of this reaction is perhaps to be preferred.

The formation of heterocyclic compounds by the reaction of ethynyl ketones with hydrazine, hydroxylamine, etc., has already been described (Bowden and Jones, *J.*, 1944, 953). The ester (III) gave with hydrazine and hydroxylamine the crystalline esters (XII) and (XIII), respectively, the reactions being smoother than those involving ethynyl ketones because of the greater stability of (III) towards alkaline reagents. Diazomethane also reacted readily with (III) in ethereal solution to yield (XIV) in good yield [its structure was not proved rigidly, and it may be the isomeric methyl 2-benzoylpyrazole-3-carboxylate. The "3-benzoylpyrazole"

obtained from diazomethane and phenyl ethynyl ketone by Bowden and Jones (*loc. cit.*) may similarly be the 2-benzoyl compound].



It was pointed out by Bowden and Jones (*loc. cit.*) that the reactions of ethynylketones in general parallel those of the hydroxymethylene derivatives of the corresponding methyl ketones, and the ethynyl ketones can often be substituted advantageously for the latter (cf. Johnson, *J.*, 1947, 346). The examples of heterocyclic syntheses given above demonstrate that αβ-acetylenic γ-keto-esters show a similar parallelism to αγ-diketo-esters, which indeed can easily be prepared from them. Although the latter are in most cases much more readily accessible (from the condensation of oxalic ester with methyl ketones) the greater reactivity of the acetylenic compounds suggests that these may occasionally be of value.

Light-absorption data for the amine adducts described are given in Table I, the values for the nearest available analogues in the 2-aminovinyl ketone series being given for comparison. Data for the corresponding enols are given in Table II. It is clear that in alcoholic solutions

TABLE I.

Light Absorption of Adducts.

Amino-keto-acid derivative.	$\lambda_{max.}$ Å.	$\varepsilon_{max.}$	Corresponding amino-ketone.[1]	$\lambda_{max.}$ Å.	$\varepsilon_{max.}$
PhCO·CH=C(NH$_2$)·CO$_2$Me	2590	4,500	PhCO·CH=CH·NH$_2$ (m. p. 70°)	2420	14,000
	3520	17,000		3240	22,000
PhCO·CH=C(NH$_2$)·CO·NH$_2$	2460	7,000	PhCO·CH=CH·NH$_2$ (m. p. 90—91°)	2420	11,000
	2560	7,000		3240	18,000
	3430	17,500			
PhCO·CH=C(NEt$_2$)·CO$_2$Me	2470	10,500	½(PhCO·CH=CH·NH·CH$_2$)$_2$	2420	11,000
	3410	22,000		2450	11,000
				3450	17,000
PhCO·CH=C(NHPh)·CO$_2$Me	2400	13,000			
	3730	19,000	PhCO·CH=CH·NHPh	2420	17,500
				2540	17,500
PhCO·CH=C(NHPh)·CO$_2$H	2400	11,000		3740	31,000
	3680	14,000			

[1] Data from Bowden, Braude, Jones, and Weedon, *loc. cit.*, and Bowden, Braude, and Jones, *J.*, 1946, 945.

TABLE II.

Light Absorption of Enols.

	$\lambda_{max.}$ Å.	$\varepsilon_{max.}$		$\lambda_{max.}$ Å.	$\varepsilon_{max.}$
PhCO·CH=C(OH)·CO$_2$Me	3110	15,000	cf. PhCO·CH=CH·CO$_2$Me(*cis*) [1]	2510	12,000
PhCO·CH=C(OH)·CO$_2$H	3115	12,500	PhCO·CH=CH·CO$_2$Me(*trans*) [1]	2350	12,000
	3340 *	9,500		2680	9,000
PhCO·CH=C(OH)·CO·NH$_2$	2230	6,000	PhC(OH)·C(OMe)=CH [1]	2250	13,500
	3240	14,000	O—CO		
PhCO·C(OH)=CH·CO$_2$H	2680	13,500			

* Inflexion.

[1] Nineham and Raphael, *loc. cit.*

these compounds exist, at any rate largely, as the vinylamine and enolic forms rather than their imino- and ketonic tautomers. The powerful auxochromic effects of the amino- and hydroxyl groups in the α-substituted β-benzoylacrylic acid derivatives correspond to those observed in the vinyl ketone series (Bowden, Braude, Jones, and Weedon, *loc. cit.*). The effect

of the carbomethoxyl, carboxyl, or carbamyl group on the position and intensity of the absorption maximum is not profound, but it is unexpectedly variable. The differences between the light absorption of the methyl ester and the amide of α-hydroxy-β-benzoylacrylic acid, and of the acid itself, are especially interesting; normally the conversion of an acid into its ester or amide has little effect on its light absorption. In these compounds however, the adjacent carboxyl or similar group clearly can interact with the hydroxyl or amino-group, possibly by hydrogen bonding, thereby modifying the mobility of its free electron pair and hence its auxochromic effect (cf. Bowden, Braude, and Jones, *J.*, 1946, 748).

As would be expected the hydroxyl group in β-hydroxy-β-benzoylacrylic acid has little effect on the light absorption; the difference between this compound and the β-methoxy-β-benzoylacrylic acid described by Nineham and Raphael (*loc. cit.*), which exists in the cyclic form, is noteworthy.

The acetylene carbinols required for this work were prepared by the method of Heilbron, Jones, and Weedon (*J.*, 1945, 81) with numerous minor modifications; the preparation of phenylethynylcarbinol is described to exemplify these and because existing physical constants apparently refer to incompletely purified materials. The acetylenic hydroxy-acids were obtained by the method of Haynes and Jones (*loc. cit.*) except that the Grignard complexes were prepared without heating (cf. Jones and Whiting, *J.*, 1949, 1423). It was found that with this modification and using ether as solvent, the method could be applied to phenylethynylcarbinol, contrary to previous experience; but when it was applied to propenylethynylcarbinol the syrupy product, though obtained in good yield and light in colour, was shown by its light absorption to contain about 50% of the rearranged isomer, from which it could not be separated. The method of carboxylating phenylethynylcarbinol described by Nineham and Raphael (*loc. cit.*) gave in our hands very variable results, apparently because of the unpredictable physical state of the precipitated sodium derivative; it could not be applied to propylethynylcarbinol. An attempt to carboxylate the dipotassium derivative of phenylethynylcarbinol, prepared by treating the carbinol with the potassium hydroxide–butyraldehyde diethyl acetal complex according to the method of Weizmann (B.PP. 573,527; 580,921; see also Bergmann, "Chemistry of Acetylenic Compounds," p. 50) also failed, the isolation of a small amount of acetylenedicarboxylic ester suggesting fission of the carbinol under these conditions.

Experimental.

(Light-absorption determinations were carried out in alcohol solutions on a Hilger medium spectrograph).

Phenylethynylcarbinol.—The apparatus consisted of a three-necked, 10-l. flask fitted with an efficient stirrer (without mercury seal) and a gas inlet tube of at least 12 mm. diameter, the whole being well insulated by immersion in cork dust. To liquid ammonia (6 l.), powdered ferric nitrate (3 g.) and sodium (10 g.) were added, and after a short interval more sodium (290 g.; ½-inch cubes). When after 20—60 minutes the colour had changed from dark blue to grey, acetylene was passed in rapidly; after some hours the colour again changed, becoming clear and black. The flow of acetylene was replaced by a slow current of nitrogen and a solution of benzaldehyde (1230 g.) in dry ether (1 l.) was added during two hours. After the flask contents had been stirred for 16 hours, ether (1·5 l.) was added, and the mixture was warmed until the greater part of the ammonia had evaporated. Ice and 6*N*-sulphuric acid in excess were added, and the aqueous layer was extracted with ether, the extract then being washed with sodium hydrogen carbonate and dried. After the removal of ether distillation of the residue at 0·3 mm. gave a number of fractions. The forerun (*ca.* 200 g.) b. p. 35—70°, consisted mainly of benzaldehyde and was discarded; fractions, b. p. 70—100°, consisting principally of the acetylenic carbinol were then obtained. Of these the middle portion had m. p. *ca.* 25—26° and was accepted; earlier and later fractions, the former containing much benzaldehyde and benzyl alcohol and the latter benzoic acid, were combined, dissolved in ether, and washed with saturated sodium hydrogen sulphite solution (the precipitated benzaldehyde addition compound being removed by filtration) and thoroughly with sodium carbonate solution. After the ethereal solution had been dried and the solvent removed the residue was distilled, fractions having m. p. 25—27° being retained; the total yield was 875 g. A specimen recovered from an attempted carboxylation by the method of Nineham and Raphael (*loc. cit.*) was free from benzaldehyde and had b. p. 94°/0·7 mm., n_D^{25} 1·5518 (supercooled), m. p. 27·5°. After crystallisation from ether–light petroleum at *ca.* −40° it formed small prisms, m. p. 28·5°, unchanged on recrystallisation from the same solvent (Jones and McCombie, *J.*, 1942, 733, give m. p. 22°; earlier workers describe this compound as a liquid).*

In the preparation of ethynylcarbinols it has been found possible to dispense with the use of a cooling bath and control of the reaction temperature. Rigorous exclusion of water by means of a mercury-sealed stirrer, soda-lime tubes, etc., is difficult and indeed somewhat hazardous because of the risk of a blockage in the latter. It is, however, preferable to decompose the sodio-complex with ammonium chloride as described by Heilbron, Jones, and Weedon (*loc. cit.*) when the carbinol is sensitive to acids or to oxidation.

3-Hydroxy-3-phenylprop-1-yne-1-carboxylic Acid (I).—Phenylethynylcarbinol (58 g.) was added during three hours to an ethereal solution of ethylmagnesium bromide [from magnesium (25 g.)], with efficient stirring and ice-cooling. The colloidal suspension obtained was stirred at 0° for a further thirty

* Cf. Clapperton and McGregor, *J. Amer. Chem. Soc.*, 1949, 71, 3234.

minutes and then poured on to an excess of solid carbon dioxide in an autoclave, which was then sealed. After 22 hours the Grignard complex was decomposed, and isolation of the acidic fraction gave a dark semi-solid mass (*ca.* 70 g.). Trituration with cold benzene gave the hydroxy-acid (48·5 g.), m. p. 84—85°, which after repeated crystallisation from benzene had m. p. 89—90° (Nineham and Raphael, *loc. cit.*, give m. p. 94—95°). Conversion into the methyl ester by refluxing a methanolic sulphuric acid solution followed by distillation at 0·01 mm. (b. p. 143°) gave yields of only 45—55%, and it was found more economical to esterify the crude acid, m. p. *ca.* 84°, with cold methanolic sulphuric acid for one week, and to oxidise the undistilled ester, obtained in 85% yield, directly to methyl β-benzoylpropiolate (II) by Nineham and Raphael's method (*loc. cit.*), the yield of pure keto-ester from the crude acid then being 55%.

Hydrogenation of Methyl β-Benzoylpropiolate.—When the keto-ester (1·1 g.) was shaken with hydrogen in methyl acetate solution in the presence of a palladium–calcium carbonate catalyst until absorption was complete (uptake 240 c.c. at 769 mm. and 18°) and the product was hydrolysed with excess of aqueous–methanolic potassium hydroxide solution for 60 hours at room temperature, isolation of the acid fraction gave β-benzoylpropionic acid (0·7 g.) as colourless plates, m. p. 114° undepressed on admixture with an authentic specimen (Somerville and Allen, *Org. Synth.*, 1933, **13**, 12, give m. p. 116°).

Methyl β-Butyrylpropiolate.—To a solution of methyl 3-hydroxyhex-1-yne-1-carboxylate (Haynes and Jones, *loc. cit.*) (5 g.) in acetone (20 c.c.) a solution of 6N-chromic acid [12 c.c.; the solution was prepared from chromic acid (100 g.), sulphuric acid (160 g.), and water (500 c.c.)] was added dropwise over a period of 20 minutes with stirring, the temperature being kept below 30° by cooling in water. The solution was stirred for a further 30 minutes and water (30 c.c.) was added; isolation of the neutral fraction with ether followed by careful fractional distillation gave the *keto*-ester (2·2 g.), b. p. 43—44°/0·02 mm., n_D^{20} 1·4511 (Found: C, 62·1; H, 6·35. $C_7H_8O_3$ requires C, 62·3; H, 6·55%), and recovered hydroxy-ester (1·2 g.), b. p. 72°/0·01 mm., n_D^{20} 1·4595. The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in yellow needles, m. p. 77—78° (Found: C, 50·25; H, 4·1. $C_{13}H_{12}O_6N_4$ requires C, 50·4; H, 4·2%).

Methyl 3-Hydroxybut-1-yne-1-carboxylate.—The crude hydroxy-acid (Haynes and Jones, *loc. cit.*) (38 g.) was esterified with methanolic sulphuric acid, giving the *ester* (27 g.), b. p. 60°/0·03 mm., 114°/12 mm., n_D^{20} 1·4579 (Found: C, 56·15; H, 6·3. $C_5H_6O_3$ requires C, 56·25; H, 6·3%).

Methyl β-Acetylpropiolate.—A solution of methyl 3-hydroxybut-1-yne-1-carboxylate (10 g.) in acetone (50 c.c.) was treated with 6N-chromic acid solution (30 c.c.) as previously described. Isolation of the product with ether, and fractional distillation gave the *keto*-ester (6·0 g.), b. p. 79°/16 mm., n_D^{20} 1·4470 (Found: C, 56·95; H, 4·6. $C_5H_6O_3$ requires C, 57·15; H, 4·8%). The 2 : 4-*dinitrophenylhydrazone* formed yellow prisms, m. p. 166°, from ethyl acetate–ethanol (Found: C, 47·75; H, 3·55. $C_{11}H_{10}O_6N_4$ requires C, 47·65; H, 3·3%).

Hydrogenation. The keto-ester (1·2 g.) in methyl acetate (20 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (100 mg.: 2%) until absorption was complete (uptake 395 c.c.). After removal of the catalyst and evaporation of the solvent distillation gave methyl lævulate (1·0 g.), b. p. 83—85°/18 mm., n_D^{20} 1·4234 (Cowley and Schuette, *J. Amer. Chem. Soc.*, 1931, **53**, 3485, give b. p. 107·7°, n_D^{20} 1·4223). The 2 : 4-dinitrophenylhydrazone formed yellow needles, m. p. 140°, from ethanol (Cowley and Schuette, *loc. cit.*, give m. p. 141—142°).

Methyl 5-Ketohex-3-en-1-yne-1-carboxylate.—A solution of methyl 5-hydroxyhex-3-en-1-yne-1-carboxylate (4 g.) (Haynes and Jones, *loc. cit.*) in acetone (30 c.c.) was treated with 6N-chromic acid (10 c.c.) at 10°. Isolation with ether and distillation gave the *keto*-ester (1·8 g.), b. p. 67°/10⁻⁴ mm., n_D^{20} 1·5140 (Found: C, 62·6; H, 5·1. $C_7H_6O_3$ requires C, 63·15; H, 5·3%). Light absorption (in alcohol): Maxima, 2600 and 2680 A.; ε = 15,000. The 2 : 4-*dinitrophenylhydrazone* formed red prisms, m. p. 185—186° (decomp.), from ethyl acetate (Found: C, 50·45; H, 3·75. $C_{13}H_{10}O_6N_4$ requires C, 50·6; H, 3·65%).

β-Hydroxy-β-benzoylacrylic Acid (IV).—6N-Chromic acid (11 c.c.) was added during 20 minutes to a solution of 3-hydroxy-3-phenylprop-1-yne-1-carboxylic acid (5 g.) in acetone (30 c.c.), the temperature being kept at 5—10°. After being stirred for a further 10 minutes the solution was diluted with water and extracted with ether, and the extract was washed with water, dried, and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 40—60°) gave the *acid* as plates, m. p. 54° (Found: C, 62·45; H, 3·8. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%). It gave a crimson ferric chloride coloration. The *quinoxaline* derivative was readily obtained by mixing ethereal solution of the acid and *o*-phenylenediamine; it formed golden-yellow plates, m. p. 262°, from methanol (Found: C, 72·85; H, 4·6. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·55%). Light absorption: Maxima at 2670, 4130, and 4350 A.; ε = 12,500, 30,000, and 27,500, respectively.

β-Hydroxy-β-acetylacrylic Acid.—Oxidation of 3-hydroxybut-1-yne-1-carboxylic acid (0·8 g.) in acetone (10 c.c.) with 6N-chromic acid (3 c.c.) at 15° followed by isolation with ether gave the crude enolic *acid* (0·5 g.) as a syrup which gave an intense crimson coloration with ferric chloride solution. It was characterised as its *quinoxaline* derivative which formed brownish prisms, m. p. 248—250°, from ethanol (Found: C, 65·8; H, 5·65. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0%). Light absorption: Maxima, 2230, 2280, 2680, and 3910 A.; ε = 30,500, 26,500, 7,000, and 17,500, respectively.

α-Hydroxy-β-benzoylacrylic Acid (*Benzoylpyruvic Acid*) (VI).—A solution of methyl β-benzoylpropiolate (0·5 g.) and potassium hydroxide (0·5 g.) in aqueous methanol was set aside at 20° for 18 hours. After dilution with water and ether extraction acidification of the aqueous phase precipitated an oil which solidified during 2 days at 0°, and was recrystallised from benzene to give the acrylic acid (0·15 g.) as plates, m. p. 151° (decomp.) (Brömme and Claisen, *Ber.*, 1888, **21**, 1132, give m. p. 156—158°).

Methyl α-Anilino-β-benzoylacrylate (VII).—Aniline (400 mg.) was added to a solution of methyl β-benzoylpropiolate (400 mg.) in dry ether (15 c.c.). After 20 hours the solution was filtered to remove a small quantity of flocculent matter and the ether was evaporated under reduced pressure. The residual oil solidified and was crystallised from aqueous methanol to give the *anilino*-ester (508 mg., 85%) as glistening golden-yellow needles, m. p. 59°, unchanged on recrystallisation from the same solvent or light petroleum (b. p. 40—60°) (Found: C, 72·8; H, 5·5. $C_{17}H_{15}O_3N$ requires C, 72·55; H, 5·4%).

Alkaline hydrolysis. A solution of the ester (0·3 g.) and potassium hydroxide (0·2 g.) in aqueous

methanol was set aside at 20° for 12 hours. Isolation of the acid fraction gave α-anilino-β-benzoylacrylic acid (VIII) (0·2 g.) as yellow needles, m. p. 164° (decomp.) [Brömme and Claisen, *loc. cit.*, give m. p. 168—170° (decomp.)].

The anilino-acid and the ester were readily hydrolysed by dilute mineral acid to the corresponding enols. A solution of the ester (100 mg.) in methanol (3 c.c.) was treated with 2N-hydrochloric acid (1 c.c.) at room temperature; the progress of the reaction was shown by the disappearance of the yellow colour. After 25 minutes water was added till a turbidity just formed; on storage methyl α-hydroxy-β-benzoylacrylate (V) (61 mg.) separated as cream, fine needles, m. p. 60°, unchanged on crystallisation from light petroleum (b. p. 40—60°) (Perkin, *J.*, 1872, **25**, 833, gives m. p. 61°; Drude, *Ber.*, 1897, **30**, 935, gives m. p. 62°).

Treatment of a solution of the anilino-acid (0·5 g.) in dioxan (15 c.c.) with 2N-sulphuric acid (8 c.c.) for 20 hours at room temperature gave, after dilution with water, α-hydroxy-β-benzoylacrylic acid (VI) (0·29 g.) which after crystallisation from benzene had m. p. 154° (decomp.), undepressed on admixture with a specimen prepared as above.

Methyl α-Diethylamino-β-benzoylacrylate.—Diethylamine (1 g.) was added to a solution of methyl β-benzoylpropiolate (1 g.) in methanol–ether (5 c.c.). After 20 hours at 20° evaporation of the solvent and distillation at 85° (bath temp.)/10^{-4} mm. gave the *amino*-ester (0·6 g.), n_D^{20} 1·6060 (Found: 69·05; H, 7·05. $C_{15}H_{17}O_3N$ requires C, 69·0; H, 7·35%).

Hydrolysis. The amino-ester (0·3 g.) in dioxan (15 c.c.) was treated with a solution of potassium hydroxide (5 c.c.; 0·4 N) at 20° for 20 hours. Acidification followed by isolation with ether gave an oil (0·2 g.) which solidified when kept, and was crystallised from benzene to give α-hydroxy-β-benzoylacrylic acid (VI) (0·1 g.), m. p. 156° (decomp.) undepressed on admixture with a specimen prepared as above. It is not known whether the amino-residue was removed in the alkaline hydrolysis or whether the amino-acid is so labile towards acid hydrolysis that this occurred almost immediately on acidifying the alkaline solution.

Methyl α-Amino-β-benzoylacrylate (IX).—To a solution of methyl β-benzoylpropiolate (2·0 g.) in methanol (10 c.c.) and ether (6 c.c.) ammonia (0·8 c.c.; *d* 0·88) was added. The temperature of the mixture rose quickly to 40°, then began to fall. At this point, after about 2 minutes, the reaction was stopped by the rapid removal of all volatile material under reduced pressure. Distillation of the residue at 50—70° (bath temp.)/10^{-4} mm. gave a viscous yellow oil (1·1 g.) which partly solidified after several weeks. Recrystallisation from aqueous methanol gave the *amino*-ester as large prisms, m. p. 40° (Found: C, 64·6; H, 5·25. $C_{11}H_{11}O_3N$ requires C, 64·35; H, 5·4%).

α-Amino-β-benzoylacrylamide (X).—Ammonia (2 c.c.; *d* 0·88) was added to a solution of methyl β-benzoylpropiolate (400 mg.) in methanol (6 c.c.). After 18 hours at 20° dilution with water gave the *amino-amide* (270 mg.) which after recrystallisation from benzene formed straw-coloured needles, m. p. 137° (Found: C, 63·5; H, 5·6. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3%). It crystallised well from aqueous methanol, but then retained water tenaciously and gave inaccurate analytical data.

Both the ester and the amide were readily hydrolysed by mineral acids to the corresponding enols. A solution of methyl β-benzoylpropiolate (200 mg.) in methanol (3 c.c.) was treated with ammonia (0·5 c.c.; *d* 0·88). The solution of the amino-ester obtained by allowing the reaction to continue for 15 minutes was acidified with 2N-sulphuric acid. Next morning the separated solid was recrystallised twice from aqueous methanol, giving methyl α-hydroxy-β-benzoylacrylate (V) as long needles, m. p. 59—60° undepressed on admixture with a specimen prepared as described above. Similarly α-amino-β-benzoylacrylamide (150 mg.), dissolved in methanol (6 c.c.) and 2N-sulphuric acid (2 ml.), gave, after 30 minutes at 20°, a crystalline precipitate of α-hydroxy-β-benzoylacrylamide (XI) which after recrystallisation from aqueous methanol formed pale cream needles, m. p. 140° strongly depressed on admixture with the starting material (Found: C, 62·85; H, 4·7; N, 7·2. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·75; N, 7·35%) [Mumm and Münchmeyer, *Ber.*, 1910, **43**, 3342, give m. p. 138° (decomp.)].

Methyl 3-Phenylpyrazole-5-carboxylate (XII).—A solution of hydrazine hydrate (0·1 g.) in methanol (2 c.c.) was added slowly to a solution of methyl β-benzoylpropiolate (0·5 g.) in methanol with ice-cooling. After dilution of the solution with water and isolation with ether the methyl ester was obtained, which after crystallisation from aqueous methanol formed prisms, m. p. 177—178° (Found: C, 65·4; H, 5·45. Calc. for $C_{11}H_{10}O_2N_2$: C, 65·35; H, 5·0%) (Buchner and Lehmann, *Ber.*, 1902, **35**, 35, give m. p. 181—182°).

Methyl 5-Phenylisoxazole-3-carboxylate (XIII).—A solution of hydroxylamine hydrochloride (0·5 g.) in methanol (5 c.c.) was neutralised with methanolic sodium methoxide (5 c.c.) and filtered from precipitated sodium chloride. A portion (8 c.c.) of the resultant solution was added to methyl β-benzoylpropiolate (0·5 g.) in methanol (5 c.c.), and the mixture was set aside for 18 hours at 20°. Isolation with ether then gave the *ester* (0·15 g.) as plates, m. p. 86—88° (Found: N, 6·65. $C_{11}H_9O_3N$ requires N, 6·9%).

Methyl 3(4?)-Benzoylpyrazole-4(3?)-carboxylate (XIV).—A solution of methyl β-benzoylpropiolate (1·0 g.) in ether (5 c.c.) was treated with an excess of ethereal diazomethane. After 18 hours at 20° evaporation of the solvent and crystallisation from aqueous methanol gave the *ester* as well-formed prisms, m. p. 138° (Found: C, 62·7; H, 4·6. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4%).

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56. *Heterogeneous Catalysis. Part I. Theoretical Basis.**

By D. A. Dowden.

In heterogeneous catalysis the rate of reaction is controlled by the formation of a chemisorbed complex which may be bound to the solid surface by ionic or covalent bonds.

If the rate is limited by the formation of a positive ion at a metal surface, the process is most favoured and fastest when the ionisation potential of the metal atom and the metal work function are both large, and when the gradient of electron level density with electron energy at the Fermi surface is large and positive. Formation of negative ions is optimum with small metal ionisation potentials and work functions but with an electron level density gradient which is large and negative.

Covalent bonding is treated qualitatively using Pauling's newer concept of transitional metal valencies, and the electron band theory, with the result that bonding appears most favoured and fastest on metals possessing vacant "atomic" *d*-orbitals, or a large density of electron levels close to the Fermi surface.

Activity in multiple-bond hydrogenation is associated with the "holes" in transitional metal *d*-bands, and falls to a very low value at those alloy or inter-metallic compound compositions where the "holes" are just full. These principles are applied to many catalytic phenomena, *e.g.*, poisoning.

Analogous ideas are applied to semi-conducting catalysts where activity is associated with the electron levels and lattice defects arising from impurity centres or non-stoicheiometry.

It is suggested that insulator catalysts, *e.g.*, γ-Al_2O_3, function through a proton-exchange mechanism which is particularly easy at cation defects.

1. Introduction.

War-time exigencies in industry yielded a variety of novel catalysts selected almost wholly by empirical methods and revealed our almost total ignorance of the precise rôle of the solid in heterogeneous catalysis.

In 1943 a survey of the relevant literature, including patents, showed either a complexity wherein one could not "see the wood for the trees" or kinetic studies for the most part uncorrelated with the electronic and geometric characteristics of the catalyst lattice. Separate small researches with limited objectives gave a pattern of results, broadly interpretable according to the "active centre" concept and its several models, but not at that time picturing details of importance for industrial catalyst design.

With the advent of the quantum theory of the covalent bond and transition state treatment of the activated complex, the active centre came to be portrayed as one surface atom, or a group of such atoms, possessing a unique configuration and orientation relative to certain substrate parameters. As long as such a centre could be represented by a portion of a normal lattice plane, the model was useful, but when special nuclei were postulated, having properties not simply related to those of the catalyst crystallite bulk, its heuristic value was severely limited.

Chemisorption of one or more of the reactants at an active region appeared as the first requisite of a solid catalyst in any heterogeneous reaction, chemisorption of the activated complex of the rate-controlling step determining the overall reaction rate. The bonding of the chemisorbed species with the surface might be, in the extreme, ionic or covalent.

A re-assessment of the catalytic problem then falls naturally into three parts: (*a*) a description of the chemisorbed particles, (*b*) a description of the active regions, and (*c*) the interactions in the group of particles plus regions.

The kinetics of homogeneous catalysis have been considerably advanced in recent years by the introduction of entities such as the free radical and the radical ions, and by the use of the Lewis viewpoint on generalised acid–base catalysis. Broad analogies, drawn between homogeneous acid-catalysed reactions and similar heterogeneous processes at the surface of some cation-defective oxide insulators containing protons, encourage the view that the same intermediate particles are active in both. Less well-defined relations suggest identical species at the surface of metals and semi-conductors (Bremner, *Research*, 1948, **1**, 281).

The electron shifts resulting in radical and ion formation reveal the catalyst crystallite as an electron source or sink and, in the presence of hydrogen-containing materials, as a potential proton reservoir. Lennard-Jones (*Trans. Faraday Soc.*, 1932, **28**, 333), Schmidt (*Chem. Reviews*, 1933, **12**, 363), and Nyrop ("The Catalytic Action of Surfaces," London, 1937) were aware of some of the implications of the former rôle. The binding electrons will be found in electronic levels and the chemisorbed particles in geometric sites which together minimise the free energy of activation and make the overall free-energy change a maximum for the bonding process.

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The electron-band concept of solids and the classical ionic-lattice theory, together, provide a reasonably adequate qualitative description of the significant electron and ion energy levels in the principal solid types while detailed application of conventional physical techniques to crystals and glasses has rapidly increased the number of known macroscopic and microscopic lattice defects.

It seemed therefore in 1943 that a definite correlation must exist between the electronic structure of solids and their catalytic activity; in fact a number of useful working rules were derived. Unfortunately it was not possible to commence experiments directed to the verification of these until 1946 (the data in the literature were equivocal). Recent publications concerning the catalytic activity of pure metals and alloys in hydrogenation and dehydrogenation reactions, and related observations on the catalytic, adsorptive, etc., properties of pure and so-called "mixed" oxides, imply a growing awareness of such relations. A partial statement of the situation has been published by Schwab (*Trans. Faraday Soc.*, 1946, **42**, 689) and Garner (*J.*, 1947, 1239).

This paper describes some present ideas on the subject as an interim report on a unitary theory of catalysis (Dowden, *Research*, 1948, **1**, 239).

2. The Geometry of the Catalyst Particle.

All bulk catalysts are aggregates of an entity which is taken to be a crystallite in normally crystalline materials (*e.g.*, metals) but a glassy or gel-like particle in amorphous catalysts derived from glass-forming constituents. These ultimate particles are the units affecting catalysis and possess, it is assumed, the following additional characteristics: (i) The volume properties and the surface properties (per unit surface) are identical with those of the massive material. (ii) Defective and ordered or disordered states, when present in the virgin catalyst lattice, exist unmodified right up to the solid–gas interface unless tending to equilibrate with the gas phase. (iii) Single-phase multicomponent catalysts, macroscopically homogeneous, have no excess or deficiency of any component in the surface at equilibrium. Thus, in an equilibrium copper–nickel solid solution, there is no copper enrichment at the surface. (iv) The particles are bounded by essentially plane surfaces.

It should be noted that (i) probably fails below some small particle size while (ii) may not be exactly true even at equilibrium in view of the asymmetry at the surface.

At temperatures above absolute zero, in addition to vibratory heat motion, a small fraction of the lattice ions are displaced from their lattice positions to yield Frenkel and Schottky defects (see section 10). Catalysts prepared below the Tammann temperature ($\frac{1}{2}$ × m. p. in °K.) may have a concentration of such defects considerably in excess of the equilibrium value.

3. Specific Area of the Solid.

The catalysed reaction proceeds at a gas–solid interface so that its rate must be a direct function of the specific area (area per unit weight) of the catalyst. Diffusion may limit effective reaction to a fraction of the total surface, but if the available area remains proportional to the total then activity per unit catalyst weight is proportional to specific area; this has been demonstrated experimentally (*e.g.*, Siller, *J. Amer. Chem. Soc.*, 1943, **65**, 431).

Catalyst modification can alter both specific area and activity per unit area (specific activity), and the two must be evaluated separately. The factors controlling development or maintenance of a given specific area are usually less critical and better known than those affecting specific activity; they will not be discussed further.

4. Specific Activity.

Activity per unit area, a function of catalyst composition and state, is independent of specific area within the approximations of section 2.

When the system is chosen so that volume and surface diffusion steps are very fast a catalytic reaction can be formally presented as (i) chemisorption of one or more reactants, (ii) reactions in the total adsorbate plus surface complex, and (iii) desorption of the products.

In the stationary state the overall reaction rate (V_s) is that of the slowest step.

$$V_s = k \times (A)^m \times (B)^n \times \ldots . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where letters in parentheses represent surface or volume concentrations of those species yielding the activated complex.

The rate constant k equals

$$K\frac{kT}{h}\exp.[-\Delta F^{\circ}/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

or

$$K\frac{kT}{h}\exp.[-\Delta U^{\circ}/kT + \Delta S^{\circ}/k] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

K is the transmission coefficient, ΔF°, ΔU°, ΔS° are the Helmholtz free energy, intrinsic energy, and entropy of formation, respectively, of the complex. k is the Boltzmann constant and h is Planck's constant.

Ideally the reaction mechanism can be defined and ΔF° evaluated at the slowest step. In practice the trends in ΔF° at the likely controlling steps must be predicted from semi-empirical rules.

(a) *Chemisorption.*—When adsorption or desorption is the limiting process the Lennard-Jones (*loc. cit.*) free-energy diagram illustrating activated adsorption is informative (see Fig. 1, where only electronic entropy contributions are included).

FIG. 1.

Free energy changes in the sorbed state. Only electronic entropy changes included. Positive ion formation.

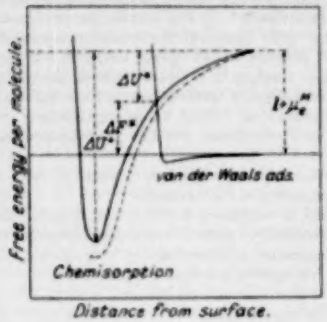
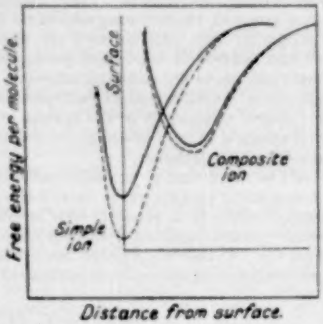


FIG. 2.

Free energy changes for a reaction in the adsorbed state.



The van der Waals adsorption free energies of a substrate are generally small, their differences still less at similar sites on a series of catalyst surfaces, so that the free energy of activation depends chiefly on the contour of the chemisorption curve, the value of the chemisorption free energy, and the distance between the two minima. On catalysts of the same solid type, if the change in force law is small, ΔF° decreases as the chemisorption free energy increases or when the distance between the equilibrium van der Waals and chemisorption positions diminishes. Active centres must therefore be associated with adsorption sites, the geometry of which requires the minimum movement of the mass centre of the particle during the transition, consistent with a maximum chemisorption free energy. Desorption free energy of activation, being the sum of ΔF° and the chemisorption free energy, can be made smaller only by modifications simultaneously minimising both the chemisorption free energy and the distance between equilibrium positions. These conclusions are independent of the nature of the bond with the surface (cf. Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 1375).

(b) *Reactions in the Adsorbate.*—Generalisation is more difficult when reaction between adsorbed species provides the rate-controlling step, as the participants may be molecules, radicals, or ions. Nevertheless a sufficiently detailed analysis of a reaction mechanism usually reveals a unimolecular or bimolecular process as the slowest step. For example:

$$ROH + H^{+} \longrightarrow ROH_2^{+}$$

or

$$ROH_2^{+} \longrightarrow R^{+} + H_2O$$

or

$$R^{+} \longrightarrow \text{Olefin} + H^{+}$$

Where the neutral molecules are physically adsorbed, the ions are held by Coulomb forces, and each ion is partitioned between the surface and a neutral molecule at the surface (Fig. 2).

Arguments, similar to those of section (*a*), suggest that the activation free energy will be lowered as the equilibrium positions are brought closer together. Catalyst changes must move the curves in the same direction parallel to the ordinate, when the forces are purely ionic and the ions of one sign, but, the radius of the composite ion being greater, the changes will there be less than for the simple ion of smaller radius (the small ion is more correctly taken to be embedded in the catalyst surface). According to this model therefore, the activation free energies for composite or simple ion formation are lowered by decreasing or increasing, respectively, the adsorption free energy of the simple ion; active centres can be defined as sites which minimise the separation of the ions and change the adsorption free energy of the smaller ion to its lowest or highest level.

When the intermediates are adsorbed radicals (as possibly at metal surfaces), the situation can be described similarly, but free energy changes cannot be easily discussed even on simple bases.

In subsequent sections consideration will be given to those factors affecting the free energy and geometry of adsorption, since these are paramount in predicting activity trends over "homologous" series of catalysts.

5. Electron Transfer at Surfaces.

Recent studies of the electrical properties of solid–fluid interfaces emphasise the existence of electron-transfer and exchange phenomena between surface and sorbate, whereby neutral molecules can yield one or more adsorbed ions (positive and negative) or radicals, depending on the electronegativities of the surface and the molecular fragments (Seitz, *J. Appl. Physics*, **1937**, **8**, 246).

Spontaneous production of a surface dipole on adsorption happens when a normally full electron level lies above a normally empty level. If the donating level lies below the acceptor level then an activation energy is required.

There are at least five pre-requisites of electron-transfer changes:

(i) The free energy change of the overall process must be negative.

(ii) At the position of van der Waals adsorption the normally full substrate levels (minimum ionisation potential I) or empty levels (maximum electron affinity E) must be brought close to the normally empty or full levels, respectively, of the catalyst crystallite.

(iii) Either (*a*) the discrete electron levels of the isolated sorbate species must broaden as the surface is approached so that the minimum ionisation potential of the sorbate is decreased and its maximum electron affinity increased, or (*b*) the levels may remain discrete even at the surface, but I and E change as in (*a*).

(iv) The catalyst crystallite must possess vacant or occupied levels capable of accepting or donating electrons to form the activated complex [another aspect of (ii)].

(v) The potential barrier separating the crystal levels and the sorbate levels, when it exists, must be permeable to electrons.

Level broadening occurs when I and E are less that the inner potential of the crystal, providing that the corresponding levels interact with a quasi-continuous band of levels in the solid.

The inner potentials of metals range from 7·3 ev. (K) to 16 ev. (Ni) and seem to fall, as far as they have been measured, between 12 ev. and 16 ev. midway in a long period (Fowler, "Statistical Mechanics," 2nd Edn., Cambridge, 1936, p. 355). In semi-conductors and insulators similar magnitudes appear (O'Bryan and Skinner, *Proc. Roy. Soc.*, **1940**, *A*, **176**, 229).

Remembering that measured values of the inner potential are only average values for the crystal, and noting the effect of electrical image forces in reducing ionisation potentials, it is reasonable to assume that the inner potentials of the transitional elements, and of other compounds of catalytic interest, are always greater than the ionisation potentials of normal sorbates.

In typical metals the volume electron levels lying above the inner potential are always quasi-continuous, except for narrow forbidden regions confined to certain directions in some lattices, *e.g.*, those of bivalent metals. Insulators differ in having a wide region of forbidden energy levels lying between the top of the full band and the bottom of the empty band; sorbate levels cannot interact with this forbidden region. Semi-conductors have more or less localised and discrete, full or empty levels in this energy gap. Interaction between sorbate levels and

these semi-conductor levels depends on the energy, and density in energy and volume of the latter.

Juxtaposition of the relevant levels, according to (ii), is exact when the radius, ionisation potential, and electron affinity of the adsorbed particle are equal to those of a lattice atom or ion. In saturated molecules the first two characteristics are larger, and the third smaller than those of metal atoms, so that the required adjustment of levels can occur, if at all, only in special positions. Analogous remarks can be made of ionic lattices.

At absolute zero the energy levels of a metal crystal are full up to the Fermi surface of energy $-\phi$ (ϕ = metal electron work function). All levels above this are empty but above 0° K. the cut-off becomes diffuse due to thermal energy. Both vacant and full levels may correspond to eigen-functions of *s*, *p*, *d*, or mixed character.

Bound surface states of various origin may exist. These comprise levels corresponding to crossing of atomic levels (Shockley, *Phys. Review*, **1939**, **56**, 317), to variation in Madelung potential at the surface (Mott, "Electronic Processes in Ionic Crystals," Oxford, **1940**, p. 86), and to the presence of the sorbate (Lennard-Jones, *loc. cit.*; Pollard, *Phys. Review*, 1939, **56**, 324). Such states lying above the Fermi surface will be empty, those lying below will be full and in metals, because of transitions between the surface and volume levels, need not be

FIG. 3.

Energy of an electron in the potential field of the metal and the substrate positive ion.

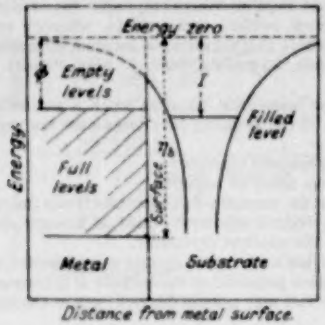
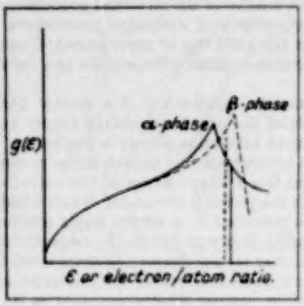


FIG. 4.

Electron level density in Hume-Rothery alloys.



considered in detail. In semi-conductors and insulators, on the other hand, surface levels where they arise may be of considerable interest.

Now that the general conditions leading to electron movement have been sketched, some special cases will be treated for various solid types on the assumption that the above conditions hold.

6. METALS.

In metal crystals the lattice electron affinity equals the lattice ionisation potential and the electron exit work function.

(i) *Positive-ion Formation.*—Positive ions are formed by transferring an electron from the highest occupied level ($-I$) of the absorbed species to the lowest unoccupied lattice level ($-\phi \simeq \mu_0^{\mathrm{M}}$) when $I^{\mathrm{L}} < \phi$ (Fig. 3).

(a) *Equilibrium.* If the sorbate at the surface is considered to be a surface phase, the electrons of which are in equilibrium with those of the metal phase through a dilute electron gas, then the ratio of ionised species in the surface phase is given by

$$ {}^{\mathrm{S}}A^{+}/{}^{\mathrm{S}}A = \frac{\mathrm{f}(A^{+})}{\mathrm{f}(A)} \exp.\,[-(I^{\mathrm{L}} + \mu_0^{\mathrm{M}})/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4) $$

where

$$ I^{\mathrm{L}} = I + \Delta U^{+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5) $$

and

$$ \mu_0^{\mathrm{M}} = -\phi - 1/6\pi^2 k^2 T^2 (\mathrm{d} \log_e g(\varepsilon)/\mathrm{d}\varepsilon)_{\varepsilon = -\phi} \quad . \quad . \quad . \quad . \quad . \quad (6) $$

(see Fowler and Guggenheim, "Statistical Thermodynamics," Cambridge, 1939, p. 472). $f(A^+)$ and $f(A)$ represent partition functions for the ionised and neutral particles respectively, $\mu_s^M = (\partial F_s^M/\partial N)_s$, equals the thermodynamic potential per metal electron per unit volume, I is the ionisation potential of the neutral particle, ΔU^+ the adsorption energy of the ion (always negative, corresponding value for the neutral particle $\simeq 0$), $g(\epsilon)$ the density in energy of electron levels per unit volume, and ϵ the metal electron energy.

The entropy change per added electron in the metal corresponding to μ_s^M is

$$(\partial S/\partial N)_T = 1/3\pi^2\hbar^2 T(\mathrm{d}\log_e g(\epsilon)/\mathrm{d}\epsilon)_{\epsilon=-\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

and can be neglected as in some thermionic work except when $(\mathrm{d}\log_e g(\epsilon)/\mathrm{d}\epsilon)_{\epsilon=-\phi}$ is large.

The electron exit work function (ϕ) is known accurately only for a few pure metals, so that it will be useful to note that it is defined by the approximate relation

$$N \simeq \int_{-\epsilon_0}^{-\phi} 2g(\epsilon)\,\mathrm{d}(\epsilon) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

N is the number of electrons per unit volume of metal and $-\epsilon_0$ the energy at the bottom of the electron band.

Other things being equal, $|\phi|$ increases as $g(\epsilon)$ increases.

The ionised electron need not enter the crystal at the Fermi energy level. For instance, in metals having holes in the d-band, surface atoms will have a certain lifetime in charged states corresponding to singly- or multiply-charged positive ions, and the donated electron will tend to enter one of these "ionised" levels. However, the Pauli principle ensures that this process from the equilibrium standpoint is equivalent to the addition of an electron at the Fermi level. Gurney (*Phys. Review*, 1935, **47**, 479) has indicated that the ionisation potential of the metal atom, rather than the work function of the metal crystal, is the better parameter to use in the treatment of ionisation at surfaces. ${}^0A^+/{}^0A$ is a maximum for a given sorbate when I^1 is a minimum and $|\mu_s^M|$ a maximum.

(b) *Geometry of the "active centre."* In a given system $|\Delta U^+|$ is a maximum (and I^1 a minimum) when the ion has acquired the greatest number of lattice atom nearest neighbours. In this state the ion takes up a position interstitially at the surface, or as near as possible to a vacant surface lattice point.

From another viewpoint, since level breadth increases exponentially as the distance between the absorbate and the surface atoms decreases, I will be a minimum when the neutral adsorbate is itself in equilibrium at a lattice defect.

Obviously such sites are most likely to exist on catalyst planes of least packing density, *e.g.*, (111) of α-iron and (110) of nickel, or at a point in the surface plane from which an atom is missing. At these centres minimum movement of mass centre occurs between the physically and chemisorbed states contributing to a minimum activation free energy; the values of parameters giving most favourable equilibrium give also the greatest ionisation velocity.

The continuity with older work on the relative energies of surface lattice points of various co-ordination number and with the more recent ideas of lattice dislocations is obvious (Mott and Nabarro, "The Strength of Solids," Physical Society, London, 1948, p. 1).

(c) *Rate.* The free energy of activation depends on the value of ΔU^+ for the system in the activated state. Reference to section 4(a) shows that it is a reasonable approximation to put the adsorption energy of the ionic activated complex proportional to ΔU^+, *i.e.* $\Delta U^\bullet = a\Delta U^+$ where a is a constant <1.

Then

$$\Delta F^\bullet \propto I + \mu_s^M - a\Delta U^+ \quad \text{or} \quad \Delta F^\bullet = b(I + \mu_s^M - a\Delta U^+) \quad . \quad . \quad . \quad . \quad (9)$$

where b is a constant and ΔU^+ now refers to the value of the ionic adsorption energy.

The corresponding entropy of activation

$$\Delta S^\bullet \propto T(\mathrm{d}\log_e g(\epsilon)/\mathrm{d}\epsilon)_{\epsilon=-\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

and for k^+, the rate constant for ionisation, we have

$$k^+ = K^+ \exp.\,[-b(I^\bullet + \mu_s^M)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where $I^\bullet = I - a\Delta U^+$ and $K^+ =$ a transmission factor.

The value of each parameter depends on the condition of the surface, that is to say whether it is bare, in unstable condition as in the induction period, or in a stationary state.

Over a "homologous" series of metals such as a series of solid solutions, and using a given sorbate, ΔU^+, ϕ and $g(-\phi)$ vary.

(d) *Factors affecting* ΔU^+ *and* I^+. In this formal presentation, the magnitude of the ionisation potential at the surface depends wholly on ΔU^+ when the forces binding the ion are taken to be purely coulombic; ΔU^+ increases as the ion gets closer to its lattice nearest neighbours. Generally the adsorbed ion diameter (D) exceeds that of the lattice atoms (d), and ΔU^+, at a vacant lattice point or interstitially, increases with increasing d since the molecule and ion can merge more closely with the metal. If ΔU^+ varies linearly with ion-surface distance, then $\Delta U^+ \propto f(d)$, where a simple model shows that fractional changes in d (when $D > d$) produce corresponding changes in the adion equilibrium distance smaller by a factor of ~ 10. Metal atom diameters, in any long period between groups 5 and 2 (*e.g.*, vanadium through nickel to zinc), show a maximum variation between successive members of 10% and an average variation of 3%; between iron and copper the maximum variation between successive members is 3·2%, between ruthenium and silver 5·1%, and between osmium and gold 4·4%. This is also the order of the change in radius of both the vacant sites in the surface planes of greatest packing density, and the interstices in the planes of least packing density, when the lattices are of the same type. Change of crystal type causes abrupt radius differences in the interstices, such as the increase in interstice radius by *ca.* 15% at the transition from the body-centred cubic to the face-centred cubic metals (iron to cobalt, molybdenum to rhodium, tungsten to iridium), and a much larger increment when hexagonal close packing occurs (zinc, ruthenium, cadmium, rhenium, osmium). It will be assumed therefore that varying d from catalyst to catalyst has negligible effect upon ΔU^+ when the metals are near neighbours and no change in lattice type is apparent. This is particularly true of the series iron, cobalt, nickel, and copper in their face-centred cubic forms.

If the linearity between ΔU^+ and ion-surface distance in the critical range is not a good approximation, then atomic diameter in the catalyst will have a somewhat larger influence on ΔU^+ than suggested above. The purely coulombic conditions are most likely to be satisfied when the ion has an inert gas structure, and when overlap is small; generally this is not so and ΔU^+ will be augmented by exchange forces of the kind described below.

Ionisation need not be simple but may produce a number of positive ions so that I must be replaced by a quantity representing a sum of dissociation energies and ionisation potentials and ΔU^+ by a sum of adsorption energies.

(e) *The electron exit work function.* The work functions of metals and alloys are largely inaccurate or unknown, but available data indicate a trend in each long period to a flat maximum in group 8, probably at nickel, palladium, and platinum where the peak in electron level density at the Fermi surface also appears.

When ϕ is not known, as in alloy systems, it cannot be calculated since it is a sum of lattice inner potential, electron kinetic energy, and intrinsic surface dipole, none of which can be estimated to the required accuracy. Generally ϕ is greatest when $g(-\phi)$ is as large as possible, which is equivalent to taking electron kinetic energy as the dominant term in the sum. Thus in alloy systems where increasing electron to atom ratio shifts the Fermi surface to regions of smaller $g(-\phi)$, it will be assumed that the rate of decrease of ϕ is larger. Certainly the rate of increase of maximum electron kinetic energy per added electron is greatly increased in such regions, *e.g.*, at the composition where a d-band becomes full or where a Hume-Rothery alloy changes phase.

In a metal crystal ϕ depends upon the indices of the surface plane and changes with lattice type; lattices and faces of densest packing seem to possess work functions slightly greater than the rest by a few tenths of an electron-volt.

The positive dipole produced at the surface by the adsorbed ions reduces ϕ until the electron transfer ceases when only a fraction of the surface is covered with ions. Clearly electropositive contaminants decrease ϕ and the equilibrium surface concentration of ions as well as the rate of ion formation; electronegative species have the opposite effect.

(f) *Electron level density.* The density of electron levels at the Fermi surface, $g(-\phi)$, attains maxima in group 8 at nickel and perhaps palladium and platinum, falling to much lower values in their alloys with copper, silver, and gold respectively, at approximately the equiatomic composition. Similar rapid changes in level density occur at the phase boundaries of Hume-Rothery alloys. Again the data are not sufficiently accurate for our purposes since they provide only average value of $(\delta \log_e g(\varepsilon)/\delta\varepsilon)_{\varepsilon=-\phi}$ over fairly wide ranges of composition whereas $(\mathrm{d} \log_e g(\varepsilon)/\mathrm{d}\varepsilon)_{\varepsilon=-\phi}$ is required at a special composition.

A large positive value of the gradient implies an appreciable positive entropy contribution

and a fall in the activation free energy; a large negative value for this parameter has the opposite effect.

While the simple band scheme provides a qualitative picture of these variables, it breaks down if pushed too far and data are too scanty to yield adequate corrections at the present time.

(g) *Change of adsorbate.* When the catalyst remains unchanged but the adsorbate varies, both I and ΔU^+ are affected. The ionisation potential of the electron removed from the adsorbate is greater or smaller depending on its bonding or non-bonding character and the environment in the molecule (Price, *Chem. Reviews*, 1947, **41**, 257). In a homologous series of molecules of increasing molecular weight, I decreases and the molecule diameter or length increases as the series is ascended. These parameters are not necessarily identical with those of the earlier considerations since in complex molecules only the smaller groupings can be accommodated at an active centre. Thus in C_nH_{2n+1}·OH adsorption the appropriate radius might be that of OH and the ionisation potential that of the non-bonding oxygen electrons; alternatively the radius of CH_2 or covalently-bound H, and the ionisation potential of the C–H bond, might be appropriate. When the reactant possesses non-localised electrons or electrons which can be excited to low lying non-localised orbitals, the relevant ionisation potential is that of the molecule as a whole. Evidently in large molecules ionisation can occur at one or more groups corresponding to multiple attachment to the surface with all its geometrical consequences. Whether the ionised electron is bonding or non-bonding the resulting ion is often unstable, as the results of mass spectroscopy often indicate (Hipple, Fox, and Condon, *Phys. Review*, 1946, **347**).

Summarising, it appears that positive-ion formation is most favoured and fastest on metals and alloys possessing the following properties: large electron exit work function, large positive value of $(\mathrm{d} \log_e g(\epsilon)/\mathrm{d}\epsilon)$ at the Fermi surface, crystallisation such that planes of least dense packing are exposed to the gas phase or such that other more densely packed planes have a high concentration of vacant sites and controlled quantities of electronegative additives.

(ii) *Negative-ion Formation.*—A negative ion is formed by removal of an electron from the highest occupied level $-\phi \simeq \mu_s^{\mathrm{M}}$ of the crystallite to the lowest unoccupied level ($-E$ = electron affinity at the surface) of the adsorbed species.

This process is the converse of that given for positive-ion formation and the fraction of ionised species in the surface phase:

$$ {}^{\mathrm{O}}B^-/{}^{\mathrm{O}}B = \frac{\mathrm{f}(B^-)}{\mathrm{f}(B)} \exp.\,[-(E' - \mu_s^{\mathrm{M}})/\boldsymbol{h}T] \quad . \quad . \quad . \quad . \quad . \quad . \quad (12) $$

where

$$ E' = E + \Delta U^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13) $$

E is the electron affinity of the isolated substrate and ΔU^- the adsorption energy of the anion, both being negative in the cases of interest.

The argument now runs much as before. Owing to the large polarisability of the negative ion there is a small image effect increasing the electron affinity at large distances from the surface, but the big increment comes into play only when the adsorbate approaches an active centre defined exactly as for positive-ion formation. A chief point of difference is the relatively large size of the anion which reduces the coulombic contributions to ΔU^- and suggests that only strongly electronegative particles form negative adions in the absence of overlap forces. The free energy of activation for ionisation is again

$$ \Delta F^\bullet \propto E + c\Delta U^- - \mu_s^{\mathrm{M}} \text{ or } \Delta F^\bullet = d(E + c\Delta U^- - \mu_s^{\mathrm{M}}), \text{ where } c \text{ and } d = \text{constants} \quad . \quad (14) $$

and the corresponding entropy

$$ \Delta S^\bullet \propto -T(\mathrm{d} \log_e g(\epsilon)/\mathrm{d}\epsilon)_{\epsilon=-\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15) $$

The rate constant for ionisation is

$$ k^- = K^- \exp.\,[-d(E + c\Delta U^- - \mu_s^{\mathrm{M}})/\boldsymbol{h}T] \quad . \quad . \quad . \quad . \quad . \quad (16) $$

The electron affinity E is unknown for most particles; the best values and the largest are available for oxygen, sulphur, and the halogens.

Negative-ion formation is fastest and most favoured on metals and alloys possessing the following properties: low electron exit work function, large negative value of $(\mathrm{d} \log_e g(\epsilon)/\mathrm{d}\epsilon)$ at the Fermi surface, all electronegative contaminants excluded, controlled quantities of electropositive additives.

(iii) *Covalent Bonding.*—Electron exchange affecting bonding through the resultant resonance

energy yields two conveniently distinguishable bond types: the metallic bond, where the bonding electrons are more or less mobile, and the covalent bond, where they are localised between the bound atoms to give a directed bond. These and intermediate bond types can arise in chemisorption.

The ratio of the work function to the first ionisation potential is about 0·5 for most elements, and atoms of metal may be deposited from the vapour on to the metal surface to form a chemisorbed layer which is an extension of the metal crystal. In the same way atoms of zinc, phosphorus, arsenic, hydrogen, and nitrogen, having first ionisation potentials between 9 and 15 ev. form solid solutions or metallic compounds with some of iron, copper, nickel, and palladium ($\phi = 4{\cdot}5$—5 ev.). The intermediate chemisorbed state cannot differ markedly from the equivalent two-dimensional solid solution, and will possess bond character of the same kind as the bulk solution, modified by the asymmetry at the interface. Similarly a gas such as carbon monoxide forms a surface complex in which the bond approximates to that in the metal carbonyls. Morris and Selwood (*J. Amer. Chem. Soc.*, 1943, **65**, 2245) observed magnetic changes on poisoning a metallic nickel catalyst with mercury, lead, and carbon monoxide, which parallel those expected on formation of solid solutions or nickel carbonyl, and support such a correspondence. Most radicals and unsaturated molecules have ionisation potentials in the above range or smaller, and homopolar bonding is expected.

Electron exchange to cause covalent bonding occurs between levels of the catalyst–substrate complex of comparable energy; moreover, since a condition of resonance is that the extreme neutral and ionic forms must involve only small displacements of the nuclei, the geometric properties already given for an active centre are optimum here also. Other things being equal, the adsorption free energy will be proportional to the adsorption energy of the radical or molecule, *i.e.*, to the additional resonance energy of the system.

(a) *Metallic bonding.* If interactions of substrate levels with all metal levels are considered qualitatively, in a molecular-orbital approximation where the metal volume levels remain mainly unaffected, it appears that a number of electrons equal to the loosely bound (" valency ") electrons of the substrate, must be promoted to the lowest, unfilled, essentially metallic level of the complex. These anti-bonding electrons must therefore be accommodated at the Fermi surface and this will be accomplished most easily when the difference in energy between the metal work function and the substrate ionisation potential at the surface is a minimum and when the energy density of levels at the Fermi surface is large (compare a copper or zinc atom alloying with a nickel surface). A physically absorbed, large saturated molecule, at a plane surface without defects, possesses a large ionisation potential and $I - \phi \sim 10$ ev. Homopolar-bond formation on closer approach can result only when the energy gained by the depression of the bonding levels exceeds that required to put electrons in the anti-bonding levels. Interaction produces a symmetrical divergence of bonding and anti-bonding orbitals about the unperturbed substrate levels, but since the metal levels are initially full at this energy no appreciable energy can be gained, certainly not 10 ev., and no bond can be formed. Bonding on this basis is possible only for initial levels close to the Fermi surface where the anti-bonding levels may be largely empty. The process is equivalent to the elevation of a metal electron, from a filled level near the substrate level, to the Fermi surface followed by interaction between the substrate level and the now unfilled metal level (Lennard-Jones, *loc. cit.*).

By analogy with solid solution effects, chemisorption is easiest when the substrate ionisation potential is less than or equal to approximately twice the catalyst work function. The limiting ionisation potential may be smaller or larger than this when the covalent radius of curvature of the intruding electron distribution is larger or smaller respectively than that of the metal atoms. Chemisorption of saturated molecules with I greater than this limit is possible only in special positions (active centres), as already described. Dissociation of the molecule into radicals of smaller I and possibly smaller radius (*e.g.*, hydrogen atoms) is a much more likely event. Saturated molecules (*e.g.*, H_2) and " unsaturated " molecules such as carbon monoxide, carbon dioxide, nitrogen, etc., because of their small covalent radius or that of the atoms into which they may split, can merge more into the metal and behave as though of lower ionisation potential than the same molecules *in vacuo*.

If the catalyst crystallite is sufficiently large for the filling of its electron levels to remain essentially undisturbed by the chemisorption, then the addition of the anti-bonding electrons at the Fermi surface introduces an electronic entropy contribution which has the same dependence on the gradient of electron level density as given for ionic bonding.

(b) *Localised bonding.* The localised bond properties follow most simply from Pauling's recently formulated valencies for the transitional series of metals (*Phys. Review*, 1938, **54**, 899;

Proc. Roy. Soc., 1949, *A*, **198**, 343) if electron pairing in chemisorption occurs both in the unfilled "atomic" orbitals (maximum number 2·48 per atom), and in the unused fraction of surface "bonding" orbitals (maximum number 6 per atom). The number of ligands of the surface atoms is less than that for a bulk atom by a factor of $\sim\frac{1}{2}$ and the geometry is asymmetric, so that the surface orbitals need not have the same character or distribution as those in the interior. Magnetic data (Selwood, *loc. cit.*; Dilke, Eley, and Maxted, *Nature*, 1948, **161**, 804) seem to show that the "atomic" orbitals are occupied by the electrons of chemisorbed species, although what probably happens is a rehybridisation of orbitals on the surface atoms to give the strongest bond with the substrate *s*-, *sp*-, or *p*-orbitals, while maintaining maximum metal-atom-to-metal-atom cohesion. Since *dsp*-orbital strength increases with *d*-content, one may expect strong bonds to be formed most easily where almost pure *d*-orbitals ("atomic orbitals") already exist, unused in metal–metal bonds. This means that covalent-bond formation should be favoured and fast on metals with unfilled "atomic orbitals." However it does not follow that bond strength must increase with increasing number of these vacant orbitals (estimated for interior atoms), because there will be modifying surface effects and energy limitations.

Taking the localised bond and the band models together suggests that the strongest covalent bonding of a substrate would result when the density of *d*-levels is largest compared with that of the *s*-, *p*-levels at the Fermi surface. This maximum in *d*-level density occurs close to pure nickel and its congeners in the transitional series. Copper and zinc can form bonds of comparable strength only after formation of an excited state requiring considerable energy input; actual bonds in chemisorption will therefore be weak.

(c) *Surface states* (Lennard-Jones, *loc. cit.*). At sufficiently small distances between the adsorbed particle and the metal surface, the superposition of the potential well of the particle on the potential step at the metal–gas interface produces a potential well just inside the metal, the depth of which depends on the metal–particle distance. Below a critical well depth surface states exist, which may be occupied by a substrate electron to form a one-electron bond (Pollard, *Phys. Review*, 1939, **56**, 324); pairing with a second electron from the metal is considered improbable.

This model for covalent bonding in chemisorption does not explain the decreased paramagnetism or ferromagnetism observed during chemisorption on some metals, or the apparent dependence of catalytic properties on conditions at the metal Fermi surface. Adsorption by this mechanism may occur alongside the types already treated especially when the metal conduction band is narrow.

Summarising these conclusions on covalent bond formation, it appears that the process of chemisorption is most favoured and fastest at surfaces having the following characteristics: large electronic work function, large value of $g(-\phi)$, large positive $(\mathrm{d}\log_e g(\epsilon)/\mathrm{d}\epsilon)_{\epsilon=-\phi}$ and presence at the surface of "atomic" orbitals in the Pauling sense.

(iv) *Real Bonds.*—Real bonds are formed by van der Waals, coulombic, and exchange forces acting together, all of which depend on the electronic structure of the solid, whether the adsorbate is molecule, radical, ion, atom, or activated complex. It is impossible to estimate the strength or rate of formation of a mixed bond by simple methods, and even in the case of the pure-bond types the models involving formal ionisation potentials, electron affinities, and work functions are not very satisfying. The problem deserves a thorough quantum-mechanical analysis which might eliminate a number of the hypotheses introduced above.

Apparently however positive-ion and covalent-bond formation have a similar dependence on the properties at the Fermi surface. Thus, when the rate-controlling step involves donation of an electron to the catalyst with exchange, or involves the surface concentration of a particle formed by such a process, then activity improves with increasing work function, level density, positive density gradient, or *d*-content of the bonding orbitals. There will be values of $|\phi - I'|$ and $|E' - \phi|$ at which the ionic contribution to the bond begins to predominate.

The reaction of saturated molecules or molecules of high ionisation potential is most likely to proceed, where possible, by mechanisms of the kind $C_2H_6 + H^+ \longrightarrow C_2H_5^+ + H_2$ or $C_2H_6 + H \longrightarrow C_2H_5 + H_2$ where the inert molecule is physically adsorbed (see Rideal, *Proc. Camb. Phil. Soc.*, 1939, **35**, 130) rather than by direct chemisorption with bond fission.

In reactions of low activation energy (~5 kcals. per mole) the variation of van der Waals free energy of adsorption with electronic structure, hitherto neglected, must be taken into account.

7. The Specific Activity.

The foregoing analysis of simplified models suggested a special configuration for the active centre, while electronic-band theory and valency theory led to optimum values for the electron

energy and level density at the Fermi surface. In particular when electron donation to the catalyst is involved at the rate-controlling step, " holes " in a *d*-band fulfil the electronic requirements and the free energy of activation at an active centre is a minimum. On the other hand if the rate-controlling step involves the positive ion as a reactant its concentration is a maximum under the same conditions. So far the electronic characteristics at an active centre have been taken equal to the average for the whole crystal, but, viewed from the atomic rather than the band standpoint, the holes in the *d*-band of a *d*-metal appear at lattice points as ions of short life. Mott and Jones (" Properties of Metals and Alloys," Oxford, 1940, pp. 192, 224) have inferred from magnetic data for pure nickel that either a pair of holes (Ni^{2+}) or none (Ni) are the preferred structures at a lattice point, but specific heat results fix the number at one (Ni^{+}; Mott, *Proc. Physical Soc.*, 1949, **62**, 416). In alloys having a constituent not normally possessing holes in its *d*-bands, *e.g.*, copper, zinc, or aluminium (" *s,p*-metals ") in nickel, the probabilities of a hole appearing at an *s,p*-atom or at a *d*-atom are not the same. Nicssen (*Physica*, 1939, **7**, 1011) considered that the holes appear mainly in the *d* atoms except in copper–nickel and nickel–zinc alloys where the distribution is random. At present the problem remains unsolved.

In our ignorance a number of possibilities need examination. The model involves a binary alloy system of uniform crystal size when the surface is essentially bare and electron donation to the crystal is rate-controlling.

(a) *Holes Randomly Distributed and All Available.*—When the crystals are small the total number of holes may be available for reaction, since the tunnel effect should render interior holes accessible up to *ca.* 40 A. from the surface when the barrier is small.

The rate of reaction per unit is then

$$\propto \frac{n n_d^1}{A} \exp. [-b(I^\bullet + \mu_e^\bullet)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

where n is the number of atoms in the crystal, n_d^1 the number of holes per atom in the *d*-band at temperature $T°$ K. and *s,p*-metal atomic fraction x. $\mu_e^\bullet$ is the thermodynamic potential per metal electron per unit volume in the alloy crystal and A its surface area.

(b) *Groups of* n *Holes, randomly distributed, Available only at the Surface.*—Although the tunnel effect enables an electron of suitable energy to reach all holes, the electrons considered here are not initially in the right state. The ionisation of the adsorbed species will be dependent on the powerful Coulomb field of the transient positive ion, and its effect upon the potential barrier will decline rapidly as the hole recedes from the surface due to the perfect shielding by the mobile electrons. The chance of finding a hole at a surface atom is proportional to the concentration of holes in the crystal and to the ratio of surface atoms (n_s) to the rest (n_r), *i.e.*, $\propto n_d^1 n_s/n_r$, or if the holes move in groups of y the chance of finding such a group in the surface becomes $\propto n_d^1 n_s/n_r y$ and the rate of reaction per unit area

$$\propto \frac{n_d^1 n_s}{n_r y A} \exp. [-b(I^\bullet + \mu_e^\bullet)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

(c) *As* (b) *but the Holes appear only at* d-*Atoms.*—The above equation must be multiplied by the atomic fraction of *d*-atoms giving a rate

$$\propto \frac{n_d^1 n_s}{n_r y A} (1 - x) \exp. [-b(I^\bullet + \mu_e^\bullet)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

In all the above examples the activity of an active complex has been put equal to the average for an active centre.

n_d^1 is itself a function of the alloy composition and for simplicity will be put $\simeq n_{0d}^1$ the corresponding value at 0° K., when for a binary alloy of a *d*-metal and an *s,p*-metal $n_{0d}^1 = (1 - x)n_{0d} - x({}_dn_{0s} - {}_dn_{0s}) = (1 - x)n_{0d} - xn_s$. n_{0d} and ${}_dn_{0s}$ refer to the *d*-metal and are respectively the number of holes in the *d*-band and the number of *s,p*-electrons per atom. n_{0s} is the number of *s,p*-electrons per atom of *s,p*-metal and x is the atomic fraction of *s,p*-metal. At a critical composition ($x^\bullet$), $n_{x^\bullet}^1$ becomes zero and the alloy activity can be considered in two parts corresponding to alloys having holes and those having none. If we use the (*b*) approximation and take first the *d*-metal-rich side of the critical composition, the total activity of unit area includes that of active centres with holes and active centres without holes. The activity of centres without holes is the same as that at the critical composition.

The rate of reaction at composition $x < x^\bullet$ is then

$$\propto \frac{Z}{A}\left\{\frac{n_d^1 n_s}{n_s y}\exp.\,[-b(I^\bullet + \mu_s^0)/kT] + \left(1 - \frac{n_d^1 n_s}{n_s y}\right)\exp.\,[-b(I^\bullet + \mu_s^0)/kT]\right\} \quad . \quad (20)$$

where Z is the fraction of the surface occupied by active centres. In the range of composition where there are no holes ($x > x^\bullet$) the rate

$$\propto \frac{Zns}{A}\exp.\,[-b(I^\bullet + \mu_s^0)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

Since the activity term corresponding to holes in the *d*-band is such as to give a large activity, this must fall rapidly to a small value or zero (depending on the exponential containing $x^\bullet$) at the critical composition.

At temperatures above 0° K. there is a transference of electrons from the *d*-band to the *s,p*-band in alloys such as copper–nickel (Wohlfarth, *Proc. Physical Soc.*, **1948**, **60**, 300; *Proc. Roy. Soc.*, **1949**, *A*, **195**, 434) so that $n_d^1 > n_{d_0}^1$ and the sharp drop of n_d^1 to zero at the composition $x^\bullet$ is replaced by a more gradual approach of n_d^1 to zero at a slightly different critical composition $x_1^\bullet > x^\bullet$. When the reaction is such that the holes in the *d*-band are very active and the filled band is effectively inactive, then the activity of the *s,p*-metal-rich alloys at $x > x^\bullet$ will be very sensitive to small variations in n_d^1 brought about the thermal activation. Under these conditions

$$n_d^1 \propto \exp.\,(-\Delta\varepsilon/kT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (22)$$

where $\Delta\varepsilon$ is the difference in energy between the top of the *d*-band and the Fermi surface (Mott, *Phil. Mag.*, 1936, **22**, 287; Wohlfarth, *loc. cit.*).

Over alloys where the holes appear only at *d*-atoms, the initial decline in activity with increasing x is much more rapid than that given above, but reaches zero at the same value of x. Similar results obtain regardless of the valency of the *s,p*-metal in solid solution and the activity falls more quickly to zero at a smaller $x^\bullet$ with increasing Δn_s, since $\partial n_{d_0}^1/\partial x = -\Delta n_s$.

Relevant data on the alloys of *d*-metals amongst themselves are scanty and not always reconcilable with simple band theory. Here it will be assumed that the same general principles apply. In alloys containing no *d*-metal, *e.g.*, α-brass, the two metals appear to have a common *s,p*-band and the electronic structure of an active centre will be taken, in a first approximation, to be independent of nearest neighbour atom type.

The fact that vacant electron sites appear at specific atoms suggests the link between the electronic-structure effect in catalyses and the current purely geometric interpretations.

(d) *Retardation by Reactants and Products.*—The reaction rate trends given above may be said to be typical of the metal and not of the general class of catalyst–sorbate complexes. They hold for processes proceeding in a stationary state on a sparsely populated surface, or for the induction period of a reaction involving surface coverage by chemisorbed reactants or products. In a stationary state where some chemisorbed species covers an appreciable fraction of the surface, the rate-controlling step may proceed on the bare surface or it may involve the removal of the chemisorbed material itself; both situations are normally treated by the methods initiated by Langmuir. However, where the chemisorption of the retarding species involves increase of the electron : atom ratio of the crystal it affects the whole surface by reducing n_d^1 or by raising the electron energy in *s,p*-metals. In coherent catalyst crystallites of normal size the drop in activity from this cause should be small. On the other hand, when the rate-controlling step involves an attack on the retarding layer itself, the local concentration of electrons or holes at its periphery will tend to be larger or smaller respectively than in the crystal bulk, and the reaction rate may be slower than expected. That is to say the strongly chemisorbed molecules function in the same way as *s,p*-metal, and displace the rapid onset of activity in *d*-metal alloys to values of x lower than $x^\bullet$, or in *s,p*-metal alloys produce a lowered activity corresponding to a higher electron : atom ration than actually present in the bare alloy.

All the foregoing major conclusions are reversed in an obvious manner when negative-ion formation is the rate-controlling step.

8. Pure Metal and Alloy Catalysts.

In this section the rules laid down will be applied to some real catalysts. A metallic catalyst is defined as one which *in situ* in its quasi-stationary state contains metal as a separate phase regardless of form or manner of support. When there is more than one metallic constituent the resulting alloys are assumed to be homogeneous, while in the presence of several metallic

phases the total activity is taken to be a linear function of the percentage weight, specific activity, and specific area of each phase.

Metallic catalysts of industrial interest have almost-full or just-filled 3*d*-, 4*d*-, and 5*d*-bands, and our discussion shows that their activity must vary rapidly with composition in that range. The variation in physical properties is well known (Mott and Jones, *loc. cit.*). Less well known are the hydrogen solubility studies of Sieverts *et al.* (*Z. anorg. Chem.*, 1915, **92**, 329) in the silver–, gold–, and copper–palladium systems, where the solubility at low temperatures (10—100° C.) falls rapidly from the high value in palladium to almost zero at the equiatomic composition. There exist, also, less well defined properties which change with the filling of *d*-band holes and are probably associated phenomena, *e.g.*, the rate of oxidation (Pilling and Bedworth, *Ind. Eng. Chem.*, 1925, **17**, 372) and sulphuric acid attack (Irmann, *Abhandl. Inst. Metall., Aachen*, 1916, **1**, 39) on the copper–nickel alloys, the diffusion of nickel in copper (Johnson, *Metals Tech.*, Tech. Publ. No. 2007, 1946), etc. See also Uhlig (*Trans. Electrochem. Soc.*, 1944, **85**, 307) on corrosion.

(i) *Transitional Metals.*—Only the metals from chromium to zinc will be considered but the reasoning applies equally to the remaining members of the period and to the other long periods.

Calculation (Krutter, *Phys. Review*, 1935, **48**, 664; Manning, *ibid.*, 1943, **63**, 190) shows that the density of electron levels, $g(-\phi)$, increases steadily from chromium to iron. The low-temperature electronic specific-heat data of Keesom and Kurrelmeyer (*Physica*, 1940, **7**, 1003) indicate a flat in $g(-\phi)$ extending from α-iron to β-cobalt, a sharp rise between the solid solution 85 : 15 nickel–iron and pure nickel, and a rapid fall between the nickel–copper solid solutions containing 40% and 20% of nickel. Since the best recorded electron work functions may vary by as much as 0·5 ev. for a given metal only the trends in each period will be noted. There appears to be a relatively rapid increase of work function between the metals of group 5A and 8, followed by a constant or slowly increasing value up to nickel, palladium, or platinum in each period and a rapid fall to copper, zinc, etc. (Reimann, " Thermionic Emission," Chapman and Hall, London, 1934; Herring and Nichols, *Rev. Mod. Physics*, 1949, **21**, 187). Parallel changes occur in the inner potential, where it is known, and in the reciprocal of the metal interatomic distances. If the effects of increasing electron : atom ratio from copper to zinc are observed in the properties of the corresponding solid solutions (intermetallic compounds also in the copper–zinc alloys), the above trends show discontinuities at phase boundaries, and changes of slope where the gradient of $g(\epsilon)$ undergoes rapid change.

(a) *Rate controlled by positive-ion formation.* There will be a gradual increase in activity from chromium to cobalt, onset of high activity between the alloy 85 : 15 nickel–iron and pure nickel, and a sharp maximum either at pure nickel or in dilute solid solutions of iron and cobalt in nickel. Beyond nickel the activity drops almost linearly to a very low value at 40 : 60 nickel–copper (depending on the temperature and the reaction) and then decreases slowly still further to zinc.

A number of additional effects operate but it is difficult to estimate their magnitudes or to superpose them upon the general curve. Thus, according to Pauling and Ewing (*ibid.*, 1948, **20**, 112) the electron : atom ratios of both α- and β-manganese correspond to full or almost full Brillouin zones, and therefore their activities should be less than expected on simple interpolation between the activities of body central cubic chromium and α-iron [see section 8 (iii)]. In addition, the alloys and elements between pure nickel and 40 : 60 nickel–copper are ferromagnetic at those temperatures where the free metals are normally used as catalysts. This implies [section 8 (v)] the presence below the Curie temperature of an inhibiting effect, decreasing in the series cobalt, iron, and nickel, which must be included in the total assessment of activity.

(b) *Rate controlled by negative-ion formation.* The activity trend is the opposite of that discussed in (a) while the secondary variations can obviously be treated similarly.

(c) *Rate controlled by covalent-bond formation.* The table shows how the valency orbitals are occupied in the various elements according to Pauling (*Proc. Roy. Soc.*, 1949, *A*, **196**, 343).

Transitional-metal Orbitals (Pauling).

Orbital type.	Cr.	Mn.	Fe.	Co.	Ni.	Cu.	Zn.
Bonding (max. 6) filled	3·6	4·6	5·6	6	6	5·5	4·5
Atomic (max. 3) not full	0·22	1·22	2·2	1·7	0·6	Nil	Nil

The total number of singly occupied " atomic " orbitals reaches a maximum value at the alloy of approximate composition iron 77% and cobalt 23%, and falls to zero at an alloy containing nickel 40% and copper 60%. Therefore up to this latter composition *d*-orbitals are readily available at the surface to form strong bonds, but at higher electron : atom ratios only

a fraction of the " bonding " orbitals, which are themselves decreasing in number, can be used. The activity changes must parallel these given under (a) and similar filled-zone and ferromagnetic effects will be apparent.

(ii) *Alloys of* d-*Metals with* s,p-*Metals and Metalloids.*—As an element with loosely held valency electrons is added in solid solution to a transitional element with holes in the *d*-band, the decrease in activity, when positive-ion or covalent-bond formation is rate-controlling, parallels the decline in the number of holes per atom in the *d*-band of the alloy. The rate of decrease depends upon Δn_i (cf. section 7), and is larger the higher the valency of the solute *s,p*-metal. Only in a number of simple cases can the band theory be used to predict in detail the characteristics at the Fermi surface of the alloys, and in more complex alloys recourse should be had to the physical (particularly magnetic) data themselves.

In the alloy composition range where $g(-\phi)$ begins to drop rapidly, the activation energy ($\propto I^\circ + p_i^m$) of the substrate reaction begins to increase because the rise of Fermi energy per added electron increases; the electronic contribution to the entropy of activation ($\propto dg(\epsilon)/d\epsilon$ at $\epsilon = -\phi$) falls. This phenomenon occurs because of the extensive overlapping of energy levels in solids. Homogeneous reactions correspond largely to transitions between potential surfaces, in which the energy level density, and therefore also the entropy and the entropy factor, always increase with increasing energy and hence with activation energy.

The activity–composition relation holds whether the composition corresponds to an intermetallic compound or to a solid solution, and whether the range of solid solution is wide as in nickel–copper alloys, narrow as in tin–iron, very limited (iron–copper), or scarcely different from the chemisorption of the *s,p*-metal. Hydrogen, boron, carbon, nitrogen, phosphorus, and the metalloids function in the same way as the *s,p*-metals, but possible failure of the band theory when applied to their alloys and compounds suggests caution in fixing the effective valency at the normal chemical value. The effect of hydrogen in deactivating palladium (Beeck, U.S.P. 2,223,777) must be explained on this basis and the much disputed rôle of " bulk " carbide in the Fischer–Tropsch processes appears, at the least, to be that of a diluent.

When negative-ion formation is rate-controlling the activity changes are the converse of those given above.

(iii) *Hume-Rothery Alloys.*—Jones (*Proc. Roy. Soc.*, **1934**, *A*, **144**, 225) has pointed out that the phase changes occur at special electron : atom ratios, when the Fermi surface can be reduced in energy because of the greater density of electron levels available at the Fermi surface in the new phase. Sharp changes in activity must be expected at the phase boundaries associated with the electronic readjustments and with the different geometry. The geometric contribution cannot be estimated but the electronic effects follow from the theory.

Consider the brasses, beginning at pure copper and adding zinc. At pure copper the first Brillouin zone is half full, but addition of zinc in solid solution increases the electron : atom ratio, the energy of the Fermi surface and the electron-level density [at first $g(\epsilon) \propto \epsilon^{\frac{1}{2}}$]. The gradient of level density, $dg(\epsilon)/d\epsilon$, is positive but its numerical value is small compared with that at the critical composition in the copper–nickel alloys. As the Fermi surface approaches and touches the zone boundary, $g(\epsilon)$ increases more rapidly to a sharp peak and then falls off rapidly, so that the face-centred cubic structure has a decreasing value of $g(\epsilon)$ and becomes unstable with respect to the body-centred cubic structure which possesses a large increasing value of $g(\epsilon)$ at the same electron : atom ratio. The α-phase therefore rearranges to yield the β-phase, in which the level density at the Fermi surface increases, the gradient of level density changes from large negative to large positive, and the energy of the Fermi surface decreases (Fig. 4).

A similar description can be given of the changes at the boundaries of the β-phase with the γ-phase and of the γ-phase with the ε-phase.

(a) *Rate controlled by positive-ion formation.* The free energy of activation must increase up to the composition where the Fermi surface touches the zone boundary because the energy of activation increases with increase of Fermi energy and the electronic contribution to the entropy of activation is small but positive. [The gradient of $g(\epsilon)$ must be very large to make an appreciable entropy contribution since it appears in the latter as $d \log_e g(\epsilon)/d\epsilon$.] Further increase of electron : atom ratio pushes the Fermi surface up to the peak in $g(\epsilon)$, and this will be accompanied by a flattening of the rising activation free energy curve owing to a diminution in the rate of increase of the Fermi energy per added electron and to the increasing electronic entropy effect. As the Fermi surface passes under the peak of $g(\epsilon)$ the situation is similar to that in the nickel–copper alloys, at the critical composition when the *d*-band is filling up, and a rapid increase in the free energy of activation results. However in the new phase the electronic characteristics are similar to (not identical with) those in the old phase at the composition

where $g(\varepsilon)$ is just rising to its peak. Thus at the boundary of the new phase the free energy of activation is considerably lower than that at the electron-rich edge of the old phase. This activity pattern repeats itself in each new phase as long as the structure is controlled by electron : atom ratio. In the intermediate regions of mixed phases a linear relation holds between the activities of the old and new boundaries (see Schwab, *loc. cit.*).

It is worth noting that in a given phase the activity variations between crystal faces of different Miller index will be most pronounced around the maximum in $g(\varepsilon)$.

When negative-ion formation is rate-controlling the trends are the converse of those given above.

(b) *Rate controlled by covalent-bond formation.* Pauling's valencies lead one to suppose a gradual decrease of activity from copper to zinc through the brasses, but with oscillations about this average line corresponding to the phase changes. Band theory gives the same results as in (a).

(iv) *Order and Disorder in Alloys.*—Pauling and Ewing (*loc. cit.*) suggest that ordering in β-alloys may be affected by electron filling of Brillouin zones and this leads to conclusions on activity changes during ordering and disordering similar to those considered in subsection (iii). The state corresponding to a filled zone, or one filled to just past the peak in $g(\varepsilon)$, should have the lowest activity in the absence of dominating geometric factors.

(v) *Magneto-catalytic Effect.*—Hedvall's observations (see *Chem. Reviews*, **1934**, **15**, 139; *J. Physical Chem.*, **1942**, **46**, 841; "Handbuch der Katalyse," edited by Schwab, Springer, Vienna, Vol. VI, p. 578) on activity changes as catalyst temperatures pass through the Curie point receive in part a very natural explanation according to this theory. Cardwell (*Phys. Review*, **1949**, **67**, 125) has produced evidence of a small increase in the work function of pure nickel as its temperature increases through a region including the Curie point, and this together with the accompanying disorientation of the metal-electron spins indicates a change in catalytic activity. In a ferromagnetic metal at absolute zero all *d*-band holes are of one spin only and the energy required to uncouple an electron spin is $\sim k\theta_c$, where θ_c is the Curie temperature in °K. Addition of electrons to the metal (or formation of a covalent bond) near 0°K. with the lowest activation energy can occur only for electrons of one kind of spin, and in the absence of any orienting effect of the metal-electron–substrate-electron exchange energies this implies the reduction of the entropy factor by one half. Rising temperature uncouples an increasing number of spins so that the entropy factor increases and the rate constant contains a factor $(1 + \exp. - \theta_c/T)$. Above θ_c spins of both kinds can be paired in the *d*-band and the entropy contribution from this factor is a maximum; at the same time terms containing $k\theta_c$ drop out of the activation energy. Now in real polycrystalline metals the saturation magnetisation seldom falls to zero sharply at a specific temperature but "tails" to zero slowly over a finite temperature range (Gerlach, *Z. Elektrochem.*, **1939**, **45**, 151). Over this range the entropy factor increases and the activation energy decreases in the manner described, whether positive-ion, covalent-bond, or negative-ion formation is rate-controlling; this is the magneto-catalytic effect.

If the effect noted by Cardwell (*loc. cit.*) is general, then this change in work function is an additional factor; it decreases the activation energy of reactions controlled by positive ions and increases the activation energy where negative ions are dominant.

Practically the effect can best be demonstrated on alloys of low Curie point where side reactions interfere least, but these are the catalysts where the effect will be a minimum. At higher temperatures side reactions (*e.g.*, carbide formation) confuse the issue, and the reaction between hydrogen and deuterium seems most suited to this study.

(vi) *Poisons.*—Three mechanisms of catalyst poisoning must be recognised although they are not entirely independent of each other.

(a) *Change of electron work function* (cf. Nyrop, *op. cit.*). Addition of strongly electropositive substances lowers the work function and poisons reactions proceeding *via* a positive ion at the slowest step, whereas strongly electronegative reagents poison the corresponding anion-controlled processes by raising the work function. Beyond a certain range of work function both types will poison reactions involving covalently bonded intermediates.

The rate of change of work function with surface concentration of poison is greatest when the concentration is small. Since the work function appears in the rate equation as an exponential, it can be seen that this model accounts quite well for those poisoning effects which have been used as evidence for the "non-uniform" surface. According to this view, even a uniformly active surface must exhibit a proportionally greater fall in activity on chemisorption of the first traces of poison than for the later portions.

(b) *Electron-level effects.* Multivalent elements with easily removable valency electrons, *e.g.*, mercury, lead, arsenic, antimony, tin, bismuth, etc., poison by forming surface alloys with

metals having *d*-band holes, whereby the holes or orbitals are blocked with electrons. The poisoning effect is greater the larger the valency, other things being equal [cf. section (ii)]. In the Hume-Rothery-type alloys of metals without *d*-band holes, the effect of these added substances may be that of deactivation caused by a rapid rise of the Fermi energy per poisoning atom, or of activation when sufficient of the poison is added to precipitate a localised phase change with drop in free energy of activation [cf. section (iii)]. These remarks are true for reactions involving positive-ion or covalent-bond formation at the slowest step; the converse is true in an obvious way for anion formation.

A dipole must be expected at the surface under these conditions which will have an additional effect according to (a).

(c) *Steric effects.* Both (a) and (b) imply occupancy of active centres and surface coverage with all its geometric consequences.

(vii) *Special Metallic Catalysts.*—The earlier sections have described the properties of catalysts which are obviously metallic. There are other catalysts which behave as metals although the situation is more complex; two types and their possible mode of action will be described.

(a) *Reducible metal oxide plus "irreducible oxides."* Under reducing conditions, as in hydrogenation, the easily reducible metal oxide yields small metal crystals in a matrix of unreduced mixed oxides (*e.g.*, Cu in CuO.ZnO and in $CuCr_2O_4$), or the metal crystallites carry the unreduced oxides as inclusions and adhesions (*e.g.*, promoted-iron ammonia catalysts). At the same time, owing to the possibility of alloy formation between the reduced metal and the metal of the "irreducible" oxide, the free energy of that reaction is available to assist the reduction of the intransigent oxide. This holds even though the extent of alloy formation at equilibrium amounts to scarcely more than the chemisorption of the second metal. Thus with CuO.ZnO, small crystals of brass appear and the activity of copper is diminished; or in $CuCr_2O_4$ there may be a very small concentration of chromium dissolved in copper with production of holes in the copper *d*-band and an enhancement of activity. (Such catalysts are used at moderately high temperatures.)

"Alkalisation" of metal catalysts with alkali-metal compounds, such as the carbonates and hydroxides, is a common device in hydrogenations such as ammonia synthesis. Since the reactions take place at metal surfaces it seems that the function of the electro-positive metal must be to adjust the metal work function (see Brewer, *J. Amer. Chem. Soc.*, 1931, **53**, 74; 1932, **55**, 1888; *Phys. Review*, 1931, **38**, 401), the free alkali metal being supplied by a mechanism similar to that above.

(b) *"Irreducible" oxides.* In our approximation, only the oxides of beryllium, magnesium, boron, aluminium, and silicon are considered to be irreducible. Other oxides such as zinc oxide, are known to be defective in oxygen and to be excess semi-conductors even at considerable partial pressures of oxygen. At high pressures of hydrogen or carbon monoxide this reduction will be increased, although thermodynamic data show that no bulk metal phase can separate at ordinary temperatures (<1000° c.). It seems possible that the metal atoms may form what amounts to a "dilute metal" in the oxide lattice, or they may separate into some essentially metallic surface phase, so that the catalysed reaction proceeds at a metal surface. When the oxygen-defective oxide is metallic its behaviour can be described by the principles of this section, and when it is a semi-conductor by those of following sections.

9. Reaction Examples.

Unfortunately there are no known reaction mechanisms in heterogeneous catalysis, and the application of the theory to given reactions can follow only the most general lines. As far as the scanty data go, hydrogen generally reduces the work function of group 8 metals (de Boer, "Electron Emission and Adsorption Phenomena," Cambridge, 1935, p. 149), which suggests that protons exist at the surface and that hydrogenation ought therefore to provide examples of mechanisms involving positive ions. In the same way surface reactions with oxygen or the hydroxyl ion should provide examples of anion-controlled reactions.

(a) *Hydrogen Addition at Multiple Bonds.*—Suppose that saturation of multiple bonds proceeds *via* one of the following steps which is rate-controlling (H_2, R, and RH_2 physically adsorbed; R is, *e.g.*, an olefin; the rest chemisorbed):

$$\tfrac{1}{2}H_2 \longrightarrow H^+ + e \qquad \tfrac{1}{2}H_2 \longrightarrow H$$
$$R \longrightarrow R^+ + e \qquad R + H \longrightarrow RH$$
$$R + H^+ \longrightarrow RH^+ \qquad RH + H_2 \longrightarrow RH_2 + H$$
$$R^+ + H \longrightarrow RH^+$$
$$RH^+ + H_2 \longrightarrow RH_2 + H^+, \text{ etc.}$$

The rate in the ionic mechanism is either that of the formation of a positive ion, or is proportional to the stationary concentration of a positive ion. The rates and concentrations depend upon the number and characteristics of holes in the *d*-band of a transitional metal as already described (section 7) and hydrogenation activity must fall to a low value as the holes are filled. Similar behaviour is to be expected if the intermediates are covalently bonded. The results of Rienäcker on the hydrogenation of ethylene (*Z. anorg. Chem.*, 1939, **242**, 302; 1943, **251**, 60) and cinnamic acid (*J. pr. Chem.*, 1941, **158**, 95), although not clear-cut, are in general accord with this picture.

(b) *Hydrogenolysis of Bonds.*—Bremner (*Research*, 1948, **1**, 281) has attributed the large effects in the hydrogenolysis of esters to a "protonolysis," and similar steps can be postulated for some alcohols, *e.g.*, $ROH + H^+ \longrightarrow R^+ + H_2O$ (rate-controlling), followed by $R^+ + H_2 \longrightarrow RH + H^+$. The reaction rate then depends on the surface concentration of protons, and the process may be slowed down or stopped by "alkalisation" [section 8 (vii)] which reduces the stationary work function of the metal surface. Components of acidic function such as alumina and silica may act by controlling the alkali-metal concentration through equilibria equivalent to $Na_2O + Al_2O_3 \longrightarrow Na_2Al_2O_4$, etc., and it should be possible to adjust the work function of the composite surface over a wide range (see Brewer, *loc. cit.*).

Conversely hydrogenolysis should be promoted by small concentrations of electronegative reactants such as hydrogen sulphide, provided that the surface coverage is so small that complete blocking of active centres does not occur.

(c) *Anions in Copper–Nickel Alloy Oxidation.*—A class of reaction where negative ions certainly participate is the oxidation of metals, and it is interesting to note that Pilling and Bedworth (*loc. cit.*) found large changes in rate between 20% and 70% of nickel in copper–nickel alloy oxidation at high temperatures (850—1000° C.). The oxidation rate is fairly constant up to between 30 and 40% of nickel at 850° and 900°, but then begins to fall off rapidly and approaches a much lower limiting value at 60—80% of nickel, depending on the temperature.

It may be significant that this decrease in reaction velocity begins close to the composition where the *d*-band of the alloys starts to empty and suggests that the rate-controlling step in this region involves the passage of electrons from the metal Fermi surface to oxygen to form the corresponding anions.

(d) *Electron Transfer in Hydrogen Peroxide Decomposition.*—Weiss (*Trans. Faraday Soc.*, 1935, **31**, 1547) in a continuation of earlier studies on the catalysed decomposition of hydrogen peroxide (Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 332) suggests that with metal catalysts the rate-controlling step is $H_2O_2 + \text{metal electron} \longrightarrow OH^- + OH$. The theory predicts therefore that over copper–nickel alloys the decomposition rate will be fastest on copper and copper-rich alloys, falling to a lower value as the *d*-band begins to empty in the neighbourhood of 40% of nickel. This applies at hydrogen-ion concentrations where the alloys are not attacked, and on bare metal surfaces where the oxide film is not thick enough to prevent the electron transfer.

10. Semi-conductors.

Many solid catalysts employed in reactions involving reducing and oxidising gases have some metallic characteristics or are semi-conductors *in situ* in the stationary state. This is qualitatively apparent in the radical colour changes undergone by "irreducible" oxides and sulphides on activation or in use, to yield black, lustrous, or highly coloured contact masses. It is significant also that these semi-conductors are much less active, for instance in hydrogenation, than metals at the same low temperatures and are not nearly so sensitive to poisoning by sulphur and its compounds.

Unfortunately these oxide and sulphide catalysts are amorphous in the most active forms and their structure can only be guessed, whereas metal catalysts are often recognisably crystalline by ordinary techniques. The bonding of the chemisorbed species at the semi-conductor surface must nevertheless follow the same principles as with metals, but the electronic characteristics are considerably different and the already complex substrate reactions are augmented by others in the solid. A convenient classification of catalysts follows that devised for the discussion of the electrical properties, namely as intrinsic, normal, and abnormal semi-conductors (see Mott and Gurney, "Electronic Processes in Ionic Crystals," Oxford, 1940; Seitz, "Modern Theory of Solids," McGraw Hill, New York and London, 1940). The last two kinds arise most simply under hydrogenating and oxidising conditions respectively, while many oxides and sulphides can exist in both forms depending upon the partial pressure of the electronegative element in the gas phase. In the following discussion the oxide and sulphide stoicheiometric lattices are

assumed to be purely ionic; covalent and van der Waals contributions to the inter-ionic forces are neglected without, it is believed, detracting from the validity of the results which can in any case be only of a general character. If greater detail is required, then the basic ideas must be applied to special systems along the lines followed by Mott and Littleton (*Trans. Faraday. Soc.*, 1938, **34**, 485), Seitz (*Rev. Mod. Physics*, 1946, **18**, 384), and Wright (*Proc. Physical Soc.*, 1948, **60**, 13) in studies on the solid alkali and silver halides and group 2 oxides.

(i) *Positive-ion Formation.*—Production of positive ions during chemisorption at the surface occurs, as in metals, by transfer of an electron from the filled substrate level of highest energy to the empty crystal level of lowest energy. Appropriate thermodynamic potentials for the electrons in a semi-conductor are used (see Fowler, "Statistical Mechanics," Cambridge, 1936) and conclusions are formed analogous to those found for metals. Only an outline of principles and inferences is given in the succeeding sections.

(a) *Intrinsic semi-conductors* (Fig. 5). One may suppose that few catalysts function by a purely intrinsic mechanism, but it is useful to discuss this type first because it forms a basis, small modifications of which lead to the other catalyst types.

FIG. 5.

Electron levels in an insulator or intrinsic semi-conductor (idealized).

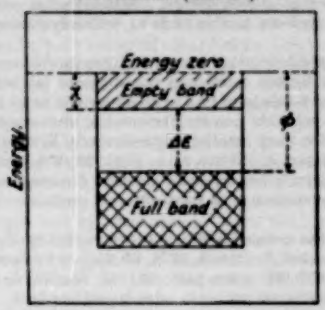
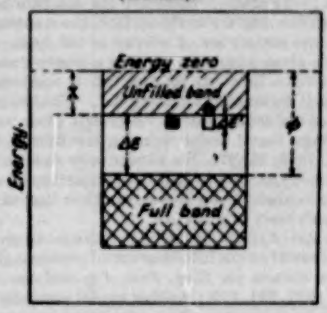


FIG. 6.

Electron levels in a normal semi-conductor (idealized).



In these solids the top (energy $= -\phi$) of the filled electron band is separated from the bottom (energy $= -\chi$) of the empty band by a forbidden energy region $\Delta\varepsilon \sim kT$, and the formation of holes in the filled band by thermal activation of electrons to empty levels is not dependent on non-stoicheiometry or impurities. At any absolute temperature T, the concentration of holes at the top of the filled band and of electrons in the empty band is $\propto \exp.[-\Delta\varepsilon/2kT]$. The holes, which may be in the filled band of the cation or anion whichever lies higher, are the acceptor levels of lowest energy, while the electrons promoted to the empty band lie in the donor levels of highest energy; both holes and electrons are mobile and can appear at the surface. For a given substrate the energy of activation for positive-ion formation is readily shown to be $\propto (I^\circ - \phi + \Delta\varepsilon/2)$ where I°, equal to $I + \Delta U^\circ$, is the ionisation potential of the activated complex and the activation energy decreases as ϕ increases and $\Delta\varepsilon$ decreases. When the catalyst lattice is ionic, $\phi = A_a e^2/a + E_a - \omega_h$, $-\chi = A_c e^2/a - I_c - \omega_e$ (see Mott and Gurney, *op. cit.*) where A_a and A_c are the Madelung potentials at anion and cation sites respectively, ω_h the polarisation energy around the electron hole, ω_e that around the excess electron, E_a is the least energy required to remove an electron from the anion *in vacuo*, I_c is the energy gained on adding an electron to the cation *in vacuo*, e is the electronic charge, and a the unit cell parameter. Therefore, $\phi - \chi = \Delta\varepsilon = (A_a + A_c)e^2/a + E_a - I_c - \omega_h - \omega_e$, and in binary compounds, where anion and cation exert the same electrovalence, $\phi - \frac{1}{2}\Delta\varepsilon \simeq (E_a + I_a)/2$ if polarisation effects are neglected. Thus on the assumption that the anion-filled band lies higher than that of the cation, the activation energy decreases as E_a and I_c increase. The full expression for $\Delta\varepsilon$ shows how it depends on the Madelung potentials and reveals that $\Delta\varepsilon$ is smaller in the surface plane owing to the reduced values of A_a and A_c in that region.

Among the catalysts of bivalent metals the effect should be apparent in cupric, mercuric, nickel, and zinc oxides where the atoms have the highest second ionisation potentials in the periodic table, and particularly in the corresponding sulphides because of the smaller negative

value of the $S^=$ electron affinity compared to that of O^-. Unfortunately these metals are multivalent or reducible and the intrinsic phenomena are masked by others, described below, arising from non-stoicheiometry; the ionic oxides having a very small potential variability of composition are insulators because of the large values of $\Delta\varepsilon$. The discussion indicates that the intrinsic semi-conductors of most use will be almost metallic in properties, and these are found amongst the metalloids and intermetallic compounds having ionic character. Their catalytic properties follow most readily by extending the arguments used for the Hume-Rothery alloys to compounds where the full and empty bands are separated by a small energy gap in all lattice directions. In this way the electronic entropy factor can be reintroduced and shown up in its dependence on $d\varepsilon(\mathbf{s})/d\mathbf{s}$, for semi-conductors and insulators, as for metals.

The value of the activation energy depends also upon ΔU° and therefore on $\Delta U^=$ which has its largest value when the substrate positive ion is adsorbed over a vacant cation point in the surface lattice. The significance of this factor will be remarked in the next section concerning a more important type of semi-conductor.

(b) *Normal semi-conductors* (Fig. 6). Here the energy bands are similar to those in intrinsic semi-conductors, but the localised occupied electron level occurs close to the bottom of the empty band and separated from it by an energy $\Delta\varepsilon'$. The number of empty localised levels in a given volume at temperature T is proportional to both the volume and energy densities of levels and to $\exp.[-\Delta\varepsilon'/2kT]$; these are the acceptor levels of lowest energy. Although the promoted electrons can migrate to the surface, the emptied levels are unable to do so, and only centres in or near to the surface are of interest in catalysis.

For a given adsorbate yielding a positive ion, the activation energy for chemisorption is now $\propto (I^\circ - \phi + \Delta\varepsilon - \Delta\varepsilon'/2)$ and this is minimised by the conditions noted under (a) but with additional parameters affecting $\Delta\varepsilon'$. The localised levels may be due to impurities or to a small excess of the lattice metal. Amongst oxide and sulphide non-stoicheiometric semi-conductors of the type found under reducing conditions, $\Delta\varepsilon'$ is very small (see particularly Fritsch, *Ann. Physik*, **1935**, **22**, 375, the extensive review by Meyer, *Z. Elektrochem.*, **1944**, **50**, 274, and Mott and Gurney, *op. cit.*) so that the probability of substrate ionisation by electron donation to these vacated localised levels is even less than that at the surface of an intrinsic semi-conductor having the same values of ϕ and $\Delta\varepsilon$.

The loss of electronegative constituent to give the reduced lattice is accompanied by displacement of metal atoms into interstitial positions (Frenkel, *Z. Physik*, **1926**, **35**, 652) or by formation of anion defects (de Boer, *Proc. Physical Soc.*, **1937**, **49**, extra part, 59; cf. Schriel, *Z. anorg. Chem.*, **1937**, **231**, 313); neither model possesses cation vacancies to adsorb positive ions. Thus electron level energy, cation adsorption energy, and active centre requirements for positive ion formation apparently cannot be met in simple, normal semi-conductors of the zinc oxide type at the conductivity centres. However if substrate ions are formed by donation of electrons to the unreduced lattice cations, or to anion defects (producing *F*-centres), the activation energies may become reasonable. Consider a stoicheiometric zinc oxide crystallite containing its equilibrium quantity of intrinsic Schottky defects (Schottky, *Z. physikal. Chem.*, 1935, *B*, **29**, 335); cation and anion vacancies occur in equal but small concentration. Hydrogen might react with the lattice in several ways: it may yield hydroxyl ions, Zn^+, and zinc metal, or form Zn^+ or *F* centres (Mott and Gurney, *op. cit.*) with the protons adsorbed at cation defects, etc.

The proton is of course most strongly adsorbed as OH^- or when situated at a cation vacancy, but may be adsorbed with a sufficient energy at other general positions bridging anions by virtue of the powerful polarisation it produces. Substrates yielding larger positive ions require cation vacancies and, as already indicated, these are present only in small concentration in the stoicheiometric crystal and are still fewer in the reduced, semi-conducting state.

Positive-ion-forming processes can be encouraged, other things being equal, only by maintaining or increasing the concentration of cation vacancies by cutting down the extent of lattice reduction in the equilibrium state, or by adding or forming an irreducible ionic compound in which the cation defect is large and permanent. These modifications are affected simultaneously by "supporting" the semi-conducting oxide upon, or combining it as a solid solution or compound with, an irreducible oxide possessing the incomplete spinel lattice, *e.g.*, γ-Al_2O_3 (Verwey, *J. Chem. Physics*, **1935**, **3**, 592) and possibly amorphous Cr_2O_3 (cf. Visser, *Chem. Weekblad*, **1946**, **42**, 127); other suitable cation-defective reagents include the amorphous glass-like oxides such as silica and the mixed alumina–silica oxides where the network-modifying positions are empty (see section 11 on insulators).

Small amounts of sulphur cannot have a drastic effect on these lattices, and such lattices are not poisoned as are metal lattices by traces of this element. On the other hand alkali-metal

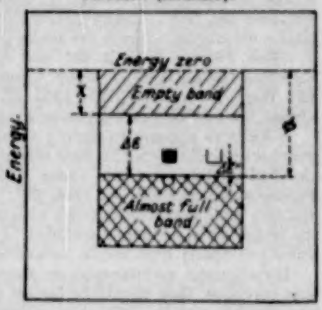
ions and the like, which block cation defects, will function as poisons in reactions controlled by the rate of formation of a positive ion or by the surface concentration of a positive ion.

(c) *Abnormal semi-conductors* (Fig. 7). Abnormal or oxidation semi-conductors have in the forbidden region an empty localised electron level close to the top of the full band and separated from it by a small energy increment $\Delta\varepsilon''$. The number of holes per unit volume in the top of the full band at any temperature T is proportional to the volume and energy level densities and to exp. $[-\Delta\varepsilon''/2kT]$, and these are the acceptor levels of lowest energy. Here the empty localised levels, existing through non-stoicheiometry or impurities, are immobile and only those at or close to the surface can function directly as acceptor levels. The holes in the full band are mobile and can migrate to the surface.

The activation energy for positive-ion formation is now $\propto (I^\circ - \phi + \Delta\varepsilon''/2)$ and is a minimum for a given substrate when ϕ is a maximum and $\Delta\varepsilon''$ is a minimum. For oxide and sulphide catalysts where conductivity ensues from a big excess of the electronegative constituent, $\Delta\varepsilon''$ is usually small compared to $\Delta\varepsilon$ (*e.g.*, Cu_2O; Juse and Kurtschatow, *Physikal. Z. Sowjetunion*, **1933**, **2**, 453; Mott and Gurney, *loc. cit.*) so that the activation energy is approximately $(I^\circ - \phi)$ and, other things being equal, this class of semi-conductor is most likely to induce positive-ion formation. The incorporation of excess of oxide or sulphide into the lattice requires an increase in the positive charge at a number of cations and the omission of cations from a number of other lattice points according to $M^+(s) + \frac{1}{2}X_2(g) \longrightarrow M^{2+}(s) + X^-(s) + h^+$. The cation vacancies ($h^+$) in the surface are the active centres at which ΔU^+ will be greatest and I° a minimum.

FIG. 7.

Electron levels in an abnormal semi-conductor (idealised).



While such non-stoicheiometric semi-conductors may be formed from appropriately chosen catalysts in oxidation reactions, they are not likely to be present in the reducing atmospheres of reactions involving hydrogen and hydrocarbons. Under the latter conditions one might choose an irreducible basis oxide and support upon it a second multivalent metal oxide so that the "valence induction" effect (Selwood *et al.*, *J. Amer. Chem. Soc.*, **1948**, **70**, 883, 2145, 2271; Report of the Pittsburgh International Conference on Surface Reactions, **1948**, p. 49) stabilises to some degree the oxidised state of the supported oxide. At least the basis oxide should possess stable cation defects, and the supported oxide also if possible.

(ii) *Negative-ion Formation.*—Negative-ion formation is most easy and fastest for a given substrate when the electrons in the catalyst are loosely held. On intrinsic semi-conductors this means when both ϕ and $\Delta\varepsilon$ are small. Subsection (i,b) (p. 260) indicates that normal semi-conductors should form negative ions readily since the electrons in the localised levels are situated relatively high in energy and are raised to the conductivity band, where they are comparatively free, with only a small energy input. Moreover there are anion vacancies to act as active centres and to increase the value of the anion adsorption energy.

Lattices which become abnormally semi-conducting in an oxidising atmosphere will affect substrate negative-ion formation by a process converse to that for positive-ion production at normal semi-conductor surfaces [see (i,b)]. Just as the latter reaction is more favoured in equilibrium and accelerated by the presence of structures with extensive stable cation defects, so should the former be assisted by stable extensively-anion-defective compounds. Not many representatives of this last kind are known at present but mention should be made of the compounds of bismuth oxide, Bi_2O_3, with lead, cadmium, and alkaline-earth oxides (Sillén and Aurivillois, *Z. Krist.*, **1939**, **101**, 483; Sillén and Sillén, *Z. physikal. Chem.*, **1941**, *B*, **49**, 27; Aurivillois, *Arkiv Kemi, Min., Geol.*, **1943**, **16**, *A*, No. 17).

(iii) *Covalent-bond Formation.*—Covalent bonding in chemisorption must follow rules fundamentally similar to those given for metals, but there exists in the more complex oxides and sulphides considerable variation on that comparatively simple theme. Thus in addition to the simple bonding, arising for instance from use of the empty orbitals at the top of an almost full anion band in an abnormal semi-conductor to form single electron bonds, there are chemisorptions of the type $CO_2(g) + O^{2-}(s) \longrightarrow CO_3^{2-}(s)$ studied by Garner (*J.*, 1947, 1239).

11. Insulators.

As already suggested in section 10(i,a), electron-transfer processes are not expected at ordinary catalyst temperatures on insulators, except to a minor extent at mechanical and intrinsic defects. The ionic insulator catalysts include chiefly the solid oxides and halides of the lower elements of groups 3, 4, and 5 of the periodic table. As a class they bring about reactions such as dehydration, isomerisation, polymerisation, cracking, etc., a most striking feature of which is the analogy with the corresponding homogeneous processes catalysed by strong acids, aluminium halides, and so on, increasingly described by carbonium- and oxonium-ion mechanisms in current literature (Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3274; Ciapetta, *Ind. Eng. Chem.*, 1945, **37**, 1210; Schmerling, *J. Amer. Chem. Soc.*, 1944, **66**, 1422; 1945, **67**, 1438, 1778; 1946, **68**, 275; Oblad and Gorin, *Ind. Eng. Chem.*, 1946, **38**, 822; Gorin, Kuhn, and Miles, *ibid.*, p. 795; Oblad, Messenger, and Brown, *ibid.*, 1947, **39**, 1462; Hansford, *ibid.*, p. 849; Bremner, *Research*, 1948, **1**, 281). It is significant in this respect that the oxide catalysts are of low activity in hydrocarbon reactions if their small water content is further reduced (see Hansford, *loc. cit.*) and if the water is looked upon as a source of protons. When pure these oxides are very poor hydrogenation, dehydrogenation, and oxidation catalysts. They are invariably colourless, as expected, and are notable glass-formers and ion exchangers; alkali-metal ions are strong poisons (Clark, Graham, and Winter, *J. Amer. Chem. Soc.*, 1925, **47**, 2748; U.S.P. 2,333,903; cf. Bremner, *loc. cit.*). Unfortunately the majority of the catalysts are amorphous with unknown lattice structures; except for active γ-alumina which has the defective spinel lattice (Verwey, *J. Chem. Physics*, 1935, **3**, 592) and related catalysts, they will be assumed to have glass-like skeletons (Zachariasen, *J. Amer. Chem. Soc.*, 1932, **54**, 3841; Hägg, *J. Chem. Physics*, 1935, **3**, 42; Weyl, *J Soc. Glass Tech.*, 1943, **27**, 133) from which the normal network-modifying ions are absent, the resulting cation vacancies and some anion bridge positions being occupied by protons.

γ-Alumina appears to occupy a unique position in the study of insulator catalysts since a number of workers confirm that activity is attributable to γ-Al_2O_3 which changes to α-Al_2O_3 at elevated temperatures (cf. Visser, *Chem. Weekblad*, 1946, **42**, 127; B.P. 571,352, 572,110; Feachem and Swallow, *J.*, 1948, 267; Fricke, Niermann, and Feichtner, *Ber.*, 1937, **70**, 2318) and they have associated activity with cation vacancies in general terms. In the following theory the properties of γ-alumina are taken to provide the clue to insulator activity which, it is asserted, arises principally from cation vacancies and possibly to a lesser extent from anion vacancies.

If carbonium- and oxonium-ion mechanisms are accepted as roughly correct for the characteristic reactions, they should be fastest at surfaces capable of forming and retaining carbonium ions through proton addition or exchange. Active surfaces must be those with cation defects, and the defects are the active centres since they possess the closest approximation to the geometry suggested in earlier sections. The free energy of chemisorption of a positive ion at a cation defect will increase as the electrostatic potential at a cation lattice point increases. In defective lattices, such as the defective spinel or a glass, it is usually assumed that the cations are distributed statistically over all the interstices of suitable radius. Although this is not likely to be an exact description at all temperatures, it does indicate that cation defects in the surface may have only a moderate life at a given lattice point. Now let the lattice contain a little water accommodated as hydroxyl groups, where the hydrogen may form hydrogen bonds with adjacent anions, then periodically, as a nearest neighbour cation site becomes empty, a proton will occupy the vacancy. At the lattice surface a cation defect has lost at least one of its anion nearest neighbours, and the deficit is made up by a substrate molecule held by polarisation forces somewhat larger than simple van der Waals forces. A proton, adjacent to the surface cation defect, now distributes itself amongst the cation point, nearest neighbour anions, and the substrate molecule according to their respective proton affinities in the solid and adsorbed phases. Thus a chemisorbed carbonium ion of definite life is formed directly from a sorbed olefinic reactant and will isomerise to the carbonium ion of greatest resonance energy (isomerisation), add to an adjacent physically adsorbed molecule (polymerisation), or to benzene and saturated hydrocarbons (alkylation), and so on. Similarly the oxonium ions derived from alcohols form carbonium ions with loss of water, and olefins are produced as the proton returns to a defect from the carbonium ion.

At low temperatures, when the mobility of the lattice cations is small, the life of surface cation defects is long, and the life of the corresponding chemisorbed complex will be controlled almost solely by the proton affinities already mentioned. On rise of temperature, cation vacancies have a much shorter existence, and the history of the chemisorbed complex will be affected by the intrusion of metal cations and the increased chance of the close approach of

another defect. As a lattice cation moves into a vacancy the proton switches *via* the surrounding anions (forming OH^-) to the lattice vacancy in its new position, the net result being that the proton tends to follow the vacancy. In the presence of sufficient water, therefore, every defect possesses at least one associated proton: hydrous γ-alumina must contain at least 2·2% of its weight as water for this to be true. Occupation by a metal cation of a surface vacancy, chemisorbing the proton–substrate complex, results in the proton following the vacancy away from, or along, the surface by the mechanism described. It may happen however that the proton remains with the substrate as a positive ion and returns to a surface vacancy at some point other than that of its origin. The effect in the case of hydrocarbon residue is that of a charge migration along the chain. High temperatures increase cation mobilities exponentially and therefore shorten the life of cation defects; at the same time the decreased equilibrium water concentration reduces the fraction of vacancies containing associated protons. Under these conditions direct scission of a substrate into a positive ion chemisorbed at a vacancy and a negative ion held by polarisation forces is increasingly probable (cf. Eyring, Hulbert, and Harman, *Ind. Eng. Chem.*, 1943, **35**, 511).

The activity of all solid insulator catalysts whether oxides or halides can be interpreted on this basis although there is no evidence as yet for the presence of cation defects in the well-known pure-halide catalysts. Activity and specificity with a given substrate depend on the surface density of cation vacancies, the electrostatic potentials at the vacancies, and their nearest neighbour anions, and the fraction of vacancies containing protons. For different substrates the effective variables are the proton affinities and the radii of molecules and fragments. Even though these parameters are not independent, it is convenient for classification to consider them separately.

(i) *Cation-vacancy Density.*—The density of cation defects should be adjustable along the lines used by Koch and Wagner (*Z. physikal. Chem.*, 1937, **38**, *B*, 295) in their studies on the silver halides. If we confine our remarks to the oxides (although they are of general applicability), this requires the solid solution of a metal oxide of high valency in the lattice of one of lower valency. The extent of such solid solution is usually small, but in the amorphous oxides it may be appreciably larger owing to the metastability implied in their glassy structures, because of the very extended surfaces where geometric restrictions will be less than in the bulk, and because of the cross-linking by hydrogen bonds. This process of cation replacement requires that a number of cations of lower valency should be omitted from the lattice; the resulting vacancies are the active centres.

Alternatively, the solute may contain an anion of lower charge than the oxygen ion, and the fluoride ion is almost ideal in that it has almost the same radius as O^{2-} and OH^-. Addition of, say, aluminium fluoride in solid solution to aluminium oxide might result in the dropping of some Al^{3+} from the lattice with creation of active vacancies. Even in favourable circumstances it is unlikely that solid solution can be pursued indefinitely: it will eventually result in the lattice breaking down into two or more solid solutions or compounds (cf. Anderson, *Proc. Roy. Soc.*, 1946, *A*, **185**, 69) some or all of which may retain cation defects. The vast number of possibilities of cation defect in compounds is too large to be covered in a discussion of this kind and recourse should be had to reviews such as those of Laves (*Z. Krist.*, 1930, **73**, 202), Strock (*Z. Krist.*, 1936, **93**, 285), Anderson (*Ann. Reports*, 1946, **43**, 104), and Wells (*Quart. Reviews*, 1948, **2**, 185).

Catalyst poisons include all those agents which occupy surface cation vacancies irreversibly, *e.g.*, alkali-metal ions introduced during preparation of γ-Al_2O_3, alumina–silica gels, etc. Generally all ions which take up "network-modifying" positions in glasses should be poisons, and those taking up "network-forming" positions should be mild promoters or deactivators depending on the reaction. Many ions can take up both sorts of position (see Weyl, *loc. cit.*), but with the present lack of understanding of catalyst preparation processes it is impossible to foretell the distribution of a particular ion in a freshly prepared catalyst (cf. Plank and Drake, *J. Colloid Sci.*, 1947, **2**, 399, 413). More empirically, it can be seen that all oxides the radius ratio (cation : anion) of which is less than 0·414 are glass-formers (Kuan-Han Sun and Silverman, *J. Amer. Ceram. Soc.*, 1942, **25**, 97) and should possess maximum activity; pure oxides outside the group BeO, B_2O_3, SiO_2, P_2O_5, and perhaps GeO_2 will possess much smaller activity on this basis. Network-formers include such oxides as Al_2O_3, TiO_2, ZrO_2, ThO_2 SnO_2, ZnO, and maybe As_2O_3, which presumably enter the network of polyhedra in the catalyst gels as in glasses; the pure oxides (except Al_2O_3) will be less active than the glass-forming group because the tendency to random linking of polyhedra, and therefore the concentrations of cation defects is less. Other reasons will be given in the next section. Similar conclusions hold for the

fluorides, or mixed lattices in which some oxygen ions have been replaced by fluorine ions; beryllium fluoride as a glass-former also yields somewhat unstable gels and is a typical borderline case. Fluorine ions however cause weakening of the polyhedra networks (Weyl, *loc. cit.*) so that fluorine-containing catalysts will be unstable compared to those containing only oxygen ions and will tend to crystallise and lose hydrofluoric acid with loss of both protons and cation vacancies at higher temperatures. Temperature stability can be improved by addition of sufficient alkali-metal or alkaline-earth oxides to stabilise the network or the defective spinel (*e.g.*, "β-alumina," Beevers *et al.*, *Z. Krist.*, 1936, **95**, 472; 1937, **97**, 59; B.P. 571,352, 572,110); such incorporations must be made in the catalyst bulk and not merely at the surface, with inevitable reduction of the number of cation vacancies. Moreover at higher temperatures ThO_2, SnO_2, ZnO, and to a lesser extent TiO_2 and ZrO_2, are reducible either completely (SnO_2), or in the semi-conductor sense (TiO_2, ZrO_2, ThO_2) and cause unwanted side-reactions which may be hindered by increasing the partial pressure of water vapour in the stationary state.

(ii) *Electrostatic Potential at a Vacancy.*—The proton affinity of an active centre is fixed, in the absence of covalent binding, by the proton affinity of the anion *in vacuo* and the electrostatic potential at the cation and anion sites. The calculations of Verwey and Heilmann (*J. Chem. Physics*, 1947, **15**, 174; 1948, **16**, 1091) show that the Madelung potential at the tetrahedral interstices is almost twice as great as that at the octahedral interstices in some spinel structures. In defective spinel lattices containing traces of water this situation can hardly be affected and the two sorts of cation vacancy will have different proton affinities with protons preferring the empty tetrahedral interstices. Thermal motion, gross structural defects, and the like will spread these proton levels out into narrow bands without displacing them appreciably. In the less crystalline glasses and " gels " a given cation defect will have a definite co-ordination number, but different defects may have co-ordination numbers varying slightly about the average, so that in the amorphous catalyst the proton affinity of the surface will vary over a wider range than at a crystal surface. Following Verwey and Heilmann (*loc. cit.*), it appears that tervalent and quadrivalent ions, in accordance with electrostatic rules, prefer octahedral interstices, while some tervalent ions such as Fe^{3+}, In^{3+}, and Ga^{3+}, along with a few bivalent ions (Zn^{2+}, Cd^{2+}), prefer tetrahedral interstices. This should provide in the defective γ-spinel structure a method for controlling the availability of the two types of vacancy; for instance, in a process deemed to require a vacancy of low proton affinity, as perhaps in a hydrocarbon reaction, the tetrahedral interstices might be blocked. Extension to amorphous catalysts is essentially simple but lack of data enforces again the use of approximations based on the properties of the relevant ions in the glasses, ion exchangers, etc.

Replacement of one or more vacancy nearest neighbour cations by one of higher charge reduces the negative potential at the vacancy and also its proton affinity. The rules affecting such substitutions have been noted above, and the possibilities depend on the co-ordination number of the site concerned. In the same way replacement of a nearest neighbour anion by one of lower charge also reduces the vacancy proton affinity. The same effects will occur regardless of the structure containing the vacancies and permit, ideally, variation of the lattice proton affinity over a wide range when polarisation is taken into account; in fact geometric restrictions arise, as mentioned in (i) (p. 263). Hansford (*loc. cit.*) and more recently Weiss (*J.*, 1948, 2164) have used Pauling's concept of electrostatic bond strength (see " The Nature of the Chemical Bond," Cornell, 1942, p. 386) to give a qualitative account of changes in the lattice " acidity," but the picture provides no model for the active centre and could be made quantitative only along lines similar to those suggested above.

Generally, increasing cation radius reduces the proton affinity at a vacancy in the pure lattice and may be another factor in the decline of catalytic activity of this kind as groups 2, 3, 4, and 5 of the periodic table are ascended.

(iii) *Proton Density.*—On the foregoing grounds ionic reaction mechanisms require protons. At low temperatures retained structural water is sufficient, but at high temperatures a partial pressure of water in the gaseous reactants may be required. Conversely, in hydrations in the liquid-phase or at high pressure, the catalyst may lose activity owing to complete hydration of the lattice with disappearance of all defects and change of lattice. The proton concentration can be raised by ion exchange with acids, by incorporating strong acids into the lattice, or by adding gaseous hydrogen to the reactants and a metal or semi-conductor to the solid phase. The last method would require a standard of control beyond that available at present.

Poisons include all substances of high proton affinity which compete with the substrate for protons and yield strongly chemisorbed positive ions (Bremner, *loc. cit.*). In the same way, molecules possessing a large affinity for carbonium ions (*e.g.*, benzene) are catalyst poisons.

Analogous reasoning leads to the conclusion that, under suitable conditions, anion-defective lattices, or lattices able to sustain an anion defect, should catalyse processes involving anion intermediates. The chief difficulty is that the known anion-defective structures (see Sillen *et al.*, *loc. cit.*; Zintl *et al.*, *Z. anorg. Chem.*, 1939, **240**, 145, 150; 1939, **242**, 79; Croatto *et al.*, *Gazzetta*, 1943, **73**, 257; 1948, **78**, 83, 95) are crystalline and not easily prepared with a large specific area.

12. Conclusions.

Ideally, the path of reaction should be predicted from the contours on an energy surface drawn to represent the change in total energy with variation of all the independent parameters. This problem is too complex to be solved at the present time, and interest has to be centred on the alteration of the total energy with variation in single parameters or small groups of parameters, called factors.

Thus we have the "geometric factor" (Ballandin, *Z. physikal. Chem.*, 1929, *B*, **2**, 289; 1929, *B*, **3**, 167; *Acta Physicochim. U.R.S.S.*, 1941, **14**, 223; Beeck, *Review Mod. Physics*, 1945, **17**, 61; also a recent review by Griffiths in "Recent Advances in Catalysis," Vol. I, p. 91, Academic Press, Inc., New York) and the "electronic structure" factor (Roginsky and Schultz, *Z. physikal. Chem.*, 1928, *A*, **138**, 21; Russell, *Nature*, 1926, **117**, 47). These factors are obviously not independent and, from the point of view of convenience in practical application, that one is preferred which shows the sharpest change with variation in catalyst activity. The preferred factor is undoubtedly that of electronic structure inasmuch as it can be related to physical measurements such as magnetic susceptibility, electrical conductivity and related phenomena, dielectric constants, etc., even when the crystal parameters are unknown or the catalyst amorphous.

The semi-empirical theories advanced in the earlier sections have been used in our laboratories at Billingham since 1943 and have permitted, it is thought, a closer insight into methods of catalyst preparation and action than was obtainable on a purely geometric basis. These studies are being continued in order to strengthen the relatively weak theoretical bases, to provide a quantitative approach, and particularly to derive experimental support for the many deductions from theory. This continuation includes not only experiments in limited systems of high purity and exact definition, but also the amassing of empirical data over wider, more ambiguous systems where the pattern of results points with more generality, although less clarity, to the desired conclusion.

Finally, I must express my thanks to my associates, particularly to Dr. J. G. M. Bremner, for many helpful discussions.

Imperial Chemical Industries (Billingham Division),
Billingham, Co. Durham. [*Received, October 14th*, 1949.]

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57. *Heterogeneous Catalysis. Part II. Hydrogenation by Binary Alloys.**

By Peter W. Reynolds.

The simple geometrical theory of catalytic activity is inadequate to explain the large difference in activity for hydrogenation between the metals of group 8 and those of group 1b. The alternative correlation of the catalytic activity with the electronic properties of the metal, discussed in Part I of this paper, associates the high activity of the group 8 metals with the holes in their 3*d*-, 4*d*-, and 5*d*-bands which are filled up in the metals of group 1b. By the examination of three series of nickel–copper catalysts it has been shown that the activity of the nickel declines in parallel with the filling of the holes in its 3*d*-band by the valency electrons of the copper, and that this occurs while the crystal lattice is expanding slightly in the direction of increased activity on the simple geometric view.

It seems reasonable to believe that the interatomic spacings in the surface planes of solid catalysts must be closely related to the parameters of molecules which react upon them (see review by Griffith, "Advances in Catalysis," 1948, vol. I, p. 91). Beeck and his co-workers (Beeck, Smith, and Wheeler, *Proc. Roy. Soc.*, *A*, 1940, **177**, 62) added considerable weight to this evidence by their work on the hydrogenation of ethylene over evaporated films of Group 8 metals. Random films of nickel, evaporated *in vacuo*, had only one-fifth of the specific activity of oriented films evaporated in a low pressure of an inert gas. The catalytically active surface

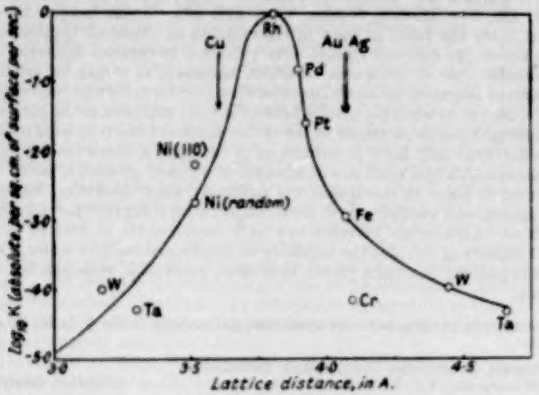
* Presented at a Discussion Meeting of the Chemical Society, London, March 17th, 1949.

was composed of spire-like prominences (Beeck and Rust, U.S.P. 2,223,777), so that the films were porous and the total surface and activity practically proportional to the weight of the deposit. In the oriented deposits the 110 planes of the nickel were parallel to the backing. In the absence of further evidence it does not seem necessary to conclude with these authors that the 110 planes were therefore preferentially exposed, but unless the presence of the inert gas had profoundly modified the structure of the metallic deposit the activity of the nickel must have been affected by its crystallographic orientation.

Following this indication Beeck (*Review Mod. Physics*, 1945, **17**, 61) has related the activity of metal catalysts in the hydrogenation of ethylene to their crystal parameters. His conclusions are reproduced in Fig. 1 where the logarithm of the reaction-velocity constant is plotted against the parameter of the metal. It is not always clear on what grounds this parameter has been selected from the alternatives available, but in the case of the face-centred cubic metals of Group 8 (nickel, rhodium, palladium, and platinum) it corresponds with the cell dimension.

FIG. 1.

Activity of metals in hydrogenation of ethylene v. *crystal parameter (Beeck).*



It seems probable that such spatial factors must play their part, but even if the suggested geometrical relations are necessary for high activity, they are certainly not sufficient. Thus copper, silver, and gold crystallise with a face-centred cubic lattice, and their parameters (Fig. 1) suggest high activities where in fact there is relatively little (copper) or practically none (silver and gold). Moreover it is always possible that these geometric correspondences are only incidental, and the prevalent tendency to hunt among the Miller indices for a plane with a promising spacing is viewed with suspicion.

In Part I of this paper an attempt was made to find alternative, more fundamental correlations between the catalytic activity and the physical structure of solids. In the simplest example of hydrogenation over metallic catalysts, the activity of Group 8 metals is attributed to the unfilled electron levels in their 3*d*-, 4*d*-, and 5*d*-bands. The relative inactivity of copper, silver, and gold is thus accounted for, because in these metals those bands are filled. Moreover, it is to be expected that any factor which tends to fill up the *d*-bands in Group 8 metals will result in a corresponding decrease in their activity.

It is therefore of particular interest to study the physical and catalytic properties of the binary alloys of Group 8 metals with one another and with the metals of Group 1b (copper, silver, and gold). Work on these systems is in progress in these laboratories. The principal effort is being directed to the study of spectroscopically-pure metallic foils, but results already obtained on industrial catalysts in the nickel–copper system support the theoretical picture given in Part I and are discussed below.

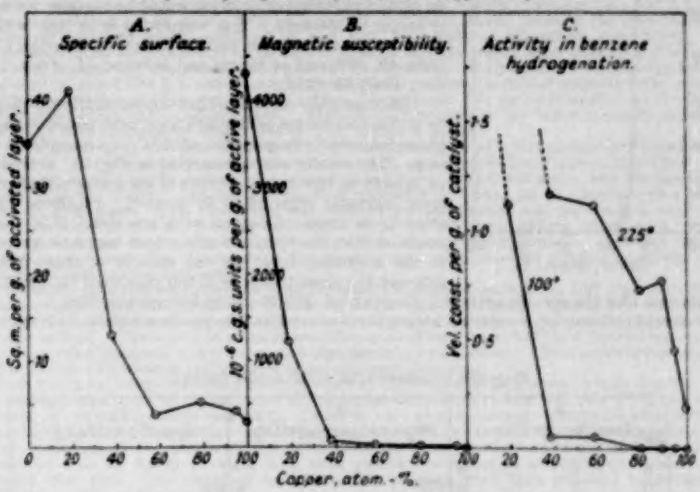
Nickel and copper both crystallise with a face-centred cubic lattice; the lattice constants are 3·517 and 3·608 A. respectively. There is a complete range of homogeneous solid solution in their binary alloys within which the crystal parameter varies almost linearly with the atomic

composition (Owen and Pickup, *Z. Krist.*, 1934, **88**, 116). Beeck's correlation suggests an increase in the specific activity of nickel by the inclusion of copper which expands the lattice. The electronic picture, on the other hand, suggests a marked fall in the activity of the nickel as the valency electrons of the added copper fill the holes in its 3*d*-band. In pure alloys at equilibrium these holes are just filled by the addition of about 60 atom-% of copper. The ferromagnetism, as measured by the large magnetic susceptibility at a fixed field strength, diminishes very rapidly at about the same composition (Kaufmann and Starr, *Phys. Review*, 1943, **63**, 445).

Data in the literature on the properties of nickel–copper catalysts are inadequate. Dupont and Piganiol (*Bull. Soc. chim.*, 1939, [v], **6**, 322) studied the influence of contamination of Raney nickel by copper on its activity for the hydrogenation of *allo*ocimene; the activity per unit weight of nickel decreased approximately linearly with increasing copper content to a low

FIG. 2.

Properties of alloy-skeletal powder nickel–copper catalysts.



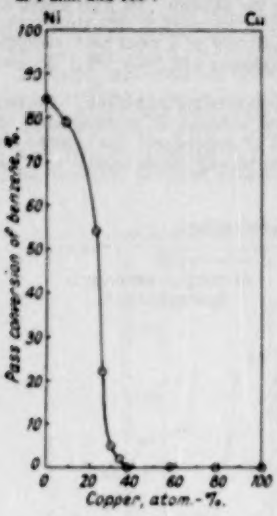
value at 50% of copper. Rienäcker (see Himmler, F.I.A.T. Review of German Science, Physical Chemistry, 1939—46, p. 97) examined nickel–copper foils for the hydrogenation of ethylene and the dehydrogenation of formic acid, and reduced nickel–copper oxide for hydrogenation of cinnamic acid. In each case the activity–composition curve exhibited a sharp step down to the low activity of copper, but the positions of these steps in the two cases were widely different. The specific surfaces of the catalysts were not measured.

In the present work, two types of alloy-skeletal nickel–copper catalysts have been examined for hydrogenation of benzene, and reduced nickel–copper oxide on kieselguhr catalysts for hydrogenation of styrene. The specific surfaces and the magnetic susceptibilities of the catalysts were determined.

Powdered nickel–copper catalysts of the Raney type were prepared by exhaustive extraction of nickel–copper–aluminium alloy powders with aqueous sodium hydroxide. The results of specific surface and magnetic susceptibility measurements in arbitrary units are summarised in Fig. 2*A* and 2*B*, and their activities in the liquid-phase hydrogenation of sulphur-free benzene at 250 atmospheres are shown in Fig. 2*C*. The highly exothermal nature of the reaction made it impossible to determine the very high activity values for the pure nickel catalysts in the apparatus employed. This series of catalysts exhibited a marked fall in specific surface with increasing copper content until at 40% of copper the specific surface had fallen to 11% of the value for pure nickel. The activity at 100°, measured per unit weight of catalyst,

FIG. 3.

Activity of foraminate nickel–copper catalysts in benzene hydrogenation at 1 atm. and 100°.



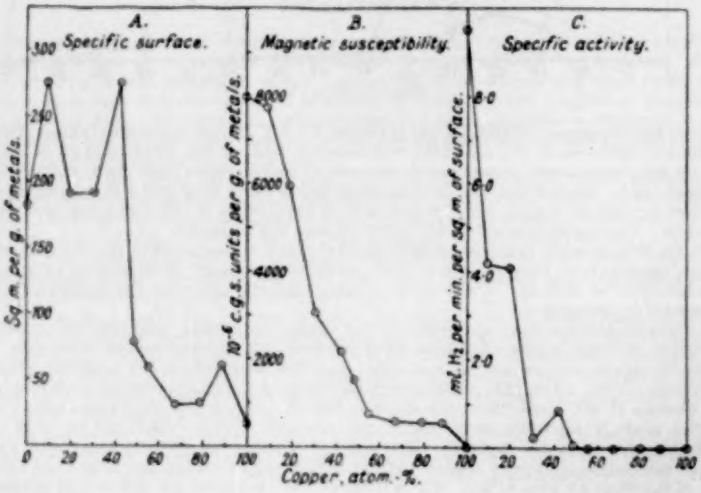
fell at a greater rate to a negligible value at the same composition. The fall in activity is thus greater than can be accounted for by the simultaneous drop in the specific surface, and it is noteworthy that it was at this composition also that the magnetic susceptibility at a fixed field strength fell to an insignificant value. Activity measurements at 225° followed the same trend, but these showed also a small decreasing residual activity at the higher copper contents, which presumably reflects the slight incompleteness of filling of the *d*-band indicated, even in alloys at equilibrium, by residual ferromagnetism at copper contents higher than the 60 atom-% where the *d*-band is ideally filled (Kaufmann and Starr, *loc. cit.*). A 100% copper catalyst prepared from spectroscopically pure metals had only one-fifth of the activity of that described above; this result suggests that an ideally pure copper catalyst would be inactive for hydrogenation of benzene. This conclusion is in line with the work of Ipatieff, Corson, and Kurbatov (*J. Physical Chem.*, 1939, **43**, 589) and of Morris and Selwood (*J. Amer. Chem. Soc.*, 1943, **65**, 2245).

Granular alloy-skeletal nickel–copper catalysts, prepared by surface activation of similar alloys, were tested in vapour-phase benzene hydrogenation at 100° at atmospheric pressure. The results are summarised in Fig. 3. Activity fell off rapidly as the copper content of the active nickel–copper layer increased from 20 to 30 atom-%; catalysts with 40 atom-% or more of copper were inactive. If it may be assumed that the specific surface and magnetic properties of the activated layer on the outside of these granules followed the same trends as in the powdered catalysts, then in this case also the specific activities disappeared with the large ferro-magnetism.

Reduced nickel–copper oxide on kieselguhr was examined in the liquid-phase hydrogenation

FIG. 4.

Properties of reduced-oxide nickel–copper catalysts.



of methanolic styrene at 30° and atmospheric pressure. The specific surface and magnetic susceptibility measurements at a fixed field strength are summarised in Fig. 4*A* and 4*B*, and the catalytic activities per unit area of active surface in Fig. 4*C*.

There is thus in all these catalysts a parallel decline in specific activity and magnetic susceptibility at a fixed field strength as the content of copper is increased. The values of both become very small or zero at 30—40 atom-% of copper in the alloy-skeletal catalysts and at 50—60 atom-% in the reduced oxide catalysts. The occurrence of the critical composition at values below the 60 atom-% which would have been expected from the properties of the pure alloys at equilibrium is undoubtedly caused by the complexity of these actual catalysts. Yet the results do show that the catalytic activity of nickel falls away in parallel with the filling of its *d*-band holes by the valency electrons of the copper, and that this occurs while the lattice is expanding in the direction of increased activity on the simple geometric view.

Experimental.

Alloy-skeletal Catalysts.—Alloy melts were prepared in graphite crucibles from Mond nickel pellets, electrolytic copper of greater than 99·99% purity, and virgin aluminium of greater than 99·5% purity. All the alloys were made to contain 50% by weight of aluminium, except those for the pure nickel and pure copper catalysts which contained 58 and 45% by weight of aluminium respectively. The homogeneous melts were chill-cast on to copper moulds, and the cooled slabs crushed and screened. Granules of approx. 1/8" diameter were selected for the foraminate catalysts, and the remaining material was ground to pass a 200 B.S. sieve mesh. (Alloy-skeletal catalysts in robust granular form, prepared by surface extraction of alloy granules, are termed " foraminates " in contradistinction to the Raney-type catalysts which are in powder form. Aluminium extraction in the latter is nearly complete.) These alloys were prepared by Messrs. Murex Ltd., Rainham, Essex.

For the Raney-type catalysts, amounts of powder containing 5 g. of active metals were added during 5 minutes to 100 ml. of a mechanically stirred boiling 30% aqueous solution of sodium hydroxide. The mixture was digested for 30 minutes, the catalyst then allowed to cool and settle, and the clear liquid decanted from the sludge. The catalyst was then re-treated by boiling for 30 minutes with a further 100 ml. of 30% alkali. This liquor also was removed by decantation, and the catalyst washed by decantation with ten 500-ml. portions of distilled water at 40°, three 150-ml. portions of " refined dry " methanol, and finally with three 100-ml. portions of sulphur-free benzene. Care was taken at every stage to prevent loss of catalyst in the decantations. The activated powders were kept under benzene and used as soon as possible.

Foraminate catalysts were prepared from the same alloys by extracting the 1/8" granules with 2% aqueous sodium hydroxide passed over them at 25 ml. per ml. of catalyst per hour at 100° until 20% of the original aluminium was removed. The progress of the extraction was followed by measuring the hydrogen evolved. The activated granules were then washed for 6 hours with cold distilled water at the same space velocity, stored under water, and used as rapidly as possible. These foraminates consisted of an activated alloy-skeletal surface layer on an unaltered alloy core.

Even the finely divided activated powders retained unextractable aluminium in their interior. The total residual aluminium in the activated 42 : 58 nickel–aluminium powder was only 2·4% and in the activated 55 : 45 copper–aluminium 6·3%. In the 20 : 30 : 50 nickel–copper–aluminium alloy, however, it was as high as 37·8%, and further extraction in molten sodium hydroxide did not greatly reduce these figures. Catalysts in the middle of the series must therefore be regarded rather as finely divided foraminates than as Raney powders, each little particle consisting of an activated surface on an unaltered alloy core. The extent of extraction was, however, more than sufficient to develop the maximum activity of the catalyst.

Reduced-oxide Catalysts.—The reduced-oxide nickel–copper on kieselguhr catalysts were prepared by precipitation from the mixed metallic nitrates. The materials taken in each case corresponded to 20% by weight of the mixed oxides on 80% of Johns Manville's " Celite 519-A." In each preparation 80 g. of iron-freed kieselguhr were suspended in 400 ml. of solution containing the requisite nickel and copper nitrates, and the metals salts were precipitated at room temperature by the stirred addition of a slight excess of solid ammonium hydrogen carbonate. The products were heated for 1 hour at 100° with stirring and then dried at 120° without filtration. The ammonium nitrate was decomposed and the basic carbonates of the metals converted into the oxides by cautious ignition in open dishes, followed by calcination for 4 hours at 400°. The powders were reduced for 4 hours at 500° in purified electrolytic hydrogen immediately before use.

Specific Surface.—The total specific surface areas of the powdered alloy-skeletal and reduced-oxide catalysts were measured by argon adsorption at the temperature of boiling liquid oxygen using the method of Brunauer, Emmett, and Teller. The results are given in Tables I and II. The areas of the powdered alloy-skeletal catalysts have been recalculated to refer to the active layer on the assumption that the whole of the residual aluminium is present in the unaltered alloy core, and these recalculated values are plotted in Fig. 2*A*.

Specific-surface measurements were not attempted on the foraminate catalysts, but it is probably safe to assume that the specific surface of the activated layer on the 1/8" granules varied with composition in the same manner as that on the particles passing a 200 B.S. mesh.

The extent of coverage of the kieselguhr in the reduced-oxide catalysts is unknown. The small contribution of the kieselguhr to the total surface has therefore been neglected in calculating the specific surface of the active metals. The area of the " Celite 519-A " used was 3·4 $m.^2$ per g., so that its maximum contribution would correspond to 17 $m.^2$ per g. of active metals. The incompleteness of reduction of the oxides has also been neglected in the calculations. The values are plotted in Fig. 4*A*.

TABLE I.

Alloy-skeletal powder catalysts.

Alloy composition, % by wt.			Residual aluminium, %	Atom-% of copper in activated layer.	Specific area.	
Ni.	Cu.	Al.			Sq. m. per g. of powder.	Sq. m. per g. of activated layer.
42	0	58	2·4	0	34	35
40	10	50	24·2	19	28	41
30	20	50	23·6	38	6·6	13
20	30	50	37·8	58	1·5	3·8
10	40	50	29·1	79	3·0	5·1
2·5	47·5	50	11·0	95	3·6	4·1
0	55	45	6·3	100	2·8	3·0

TABLE II.

Reduced-oxide-on-kieselguhr catalysts.

Analysis of material ignited at 400°.		Atom-% of Cu in reduced metals.	Specific area of reduced catalyst:	
Ni, % by wt.	Cu, % by wt.		m.²/g. of catalyst.*	m.²/g. of metals.
15·9	0·0	0·0	29	182
14·1	1·6	9·5	44	278
12·4	3·3	19·7	30	191
10·3	5·0	30·9	29	192
8·6	6·8	42·2	43	278
7·6	7·7	48·4	12	78
6·8	9·2	55·5	9·4	59
4·8	10·8	67·5	4·9	31
3·0	12·3	79·1	4·9	32
1·7	13·9	88·3	9·5	61
0·0	15·4	100·0	2·6	17

* Weighed before reduction.

TABLE III.

Magnetic susceptibilities (at 4000 Oersted) of alloy-skeletal powder catalysts.

Cu, atom-%.	Magnetic susceptibility in 10^{-6} c.g.s. units: per g. of catalyst.	per g. of active layer.	Cu, atom-%.	Magnetic susceptibility in 10^{-6} c.g.s. units: per g. of catalyst.	per g. of active layer.
0	4200	4300	79	23	39
19	830	1220	95	10	11
38	42	85	100	4	4
58	17	43			

TABLE IV.

Magnetic susceptibility (at 4000 Oersted) of reduced-oxide catalysts.

Cu, atom-%.	Magnetic susceptibility in 10^{-6} c.g.s. units: per g. of reduced catalyst.	per g. of active metals.	Cu, atom-%.	Magnetic susceptibility in 10^{-6} c.g.s. units: per g. of reduced catalyst.	per g. of active metals.
0·0	1280	8000	55·5	118	740
9·5	1140	7750	67·5	94	590
19·7	950	5950	79·1	90	560
30·9	490	3060	88·3	87	545
42·2	345	2160	100·0	0	0
48·4	244	1530			

Magnetic Susceptibility.—Magnetic susceptibilities were measured by a Sucksmith balance at a fixed field strength of 4000 Oersted. The susceptibilities of the unactivated nickel–copper–aluminium alloys were all very small, and they have been neglected in calculating the values given in Table III of the mass susceptibility per g. of active layer. The values for the reduced-oxide catalysts are given in Table IV. No measurements were made on the foraminate catalysts.

Alloy-skeletal Powder Catalysts in Liquid-phase Hydrogenation of Benzene.—Liquid-phase hydrogenation of benzene was carried out in a 250 ml. stainless steel Lindsay–Baskerville autoclave, which had been modified to prevent catalysts from being splashed into the upper parts of the stirrer mechanism and lagged to give reasonable uniformity of temperature in the reaction vessel. An internal thermocouple was also fitted.

Alloy-skeletal powders prepared, as already described, from 5-g. portions of alloy were charged with 75 ml. of an equimolar mixture of sulphur-free benzene and sulphur-free *cyclo*hexane. The apparatus was assembled, pressure-tested under nitrogen, and heated to the reaction temperature under

5 atm. of nitrogen (measured at 20°). The temperature was levelled out with the stirrer in operation, and the pressure made up to 250 atm. with electrolytic hydrogen. The rate of reaction was followed by the decreasing hydrogen pressure, and the activities of the catalysts are expressed in terms of the true rate constants (Fusek and Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 3743):

$$(2{\cdot}303\ V/wt)\ \log_{10} P_0/P \text{ (ml. per g. of catalyst per min.)}$$

where V = volume (ml.) of gas-filled space in reactor, w = weight (g.) of catalyst, P_0 = initial hydrogen pressure (atm.), and P = hydrogen pressure (atm.) after time t (min.).

With pure nickel, and the 19 atom-% copper catalyst at the higher temperature, the rate of reaction was so high that the temperature became uncontrollable; runs with reduced amounts of catalyst were unreliable. Results for the remaining catalysts at 100° and 225° are given in Table V. These results have been plotted in Fig. 2C. A catalyst prepared from copper and aluminium which were both of spectroscopic purity was also tested; the figures are included in the table.

TABLE V.

Liquid-phase hydrogenation of benzene over alloy-skeletal powders.

Copper in activated layer, atom-%.	Reaction velocity constants at 100°.	at 225°.	Copper in activated layer, atom-%.	Reaction velocity constants at 100°.	at 225°.
0	—	—	89	0·00	0·77
19	1·12	—	95	0·00	0·45
38	0·05	1·17	100	0·00	0·19
58	0·05	1·12			
79	0·00	0·73	100 (Spect. pure)	0·00	0·04

Foraminate Catalysts in Vapour-phase Hydrogenation of Benzene.—Vapour-phase hydrogenation of benzene was effected with an equimolar mixture of sulphur-free benzene and sulphur-free *cyclo*hexane fed at a total liquid space velocity of 10 hr.$^{-1}$ over 10 ml. of the foraminate catalyst maintained at 100°. The hydrogen rate was 60 l. per hour. Activities were estimated in terms of the mean pass conversion of the benzene calculated over 2-hour runs. The results are given in Table VI and plotted in Fig. 3.

TABLE VI.

Vapour-phase hydrogenation of benzene over foraminate catalysts.

Copper in active layer, atom-% ...	0	9	23	26	30	34	38	58	79	100
Pass conversion of benzene, % ...	84	79	54	22	5	2	0	0	0	0

Reduced-oxide Catalysts in Liquid-phase Hydrogenation of Styrene.—A 10% solution of redistilled styrene in "refined dry" methanol was hydrogenated at atmospheric pressure in a 100-ml. glass shaker tube immersed in a thermostat at 25°. Electrolytic hydrogen was further purified by passage through active charcoal cooled in liquid oxygen; its rate of absorption in the reactor was measured by a soap-film flowmeter. The rate of reaction was found to be independent of the styrene concentration and approximately proportional to the weight of the catalyst.

The reaction vessel was equipped with a ground-glass joint at the top and with an alternative head carrying inlet and outlet gas leads for catalyst reduction. In each experiment 0·1 g. of supported oxide was charged to the reaction vessel on its side, spread over the wall, and reduced for 4 hours at 500°. The catalyst was cooled under hydrogen, immersed in acceptor solution, and transferred in the reactor to the test apparatus. The charge was there quickly frozen by cooling it in liquid oxygen, the apparatus evacuated, and hydrogen admitted. The reaction mixture was then allowed to warm to 25° in a thermostat, and vigorously agitated by a Microid shaker.

The results are given in Table VII. The activities are recorded first as ml. of hydrogen (at 20°/760 mm.) absorbed per minute per g. of active metals, and then in terms of unit area of active metal surface by the use of the figures of Table II. The latter results are plotted in Fig. 4C.

TABLE VII.

Liquid-phase hydrogenation of styrene over reduced-oxide catalysts.

Copper in reduced metals, atom-%.	Catalytic activity in ml. of H_2 absorbed per min. per g. of active metals.	per sq. m. of active surface.	Copper in reduced metals, atom-%.	Catalytic activity in ml. of H_2 absorbed per min. per g. of active metals.	per sq. m. of active surface.
0·0	1730	9·5	42·2	235	0·84
9·5	1170	4·2	48·4	0·5	0·008
19·7	790	4·1	55·5, 67·5, 79·1,	0·0	0·000
30·9	46	0·24	88·3, 100·0		

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58. *The Heats of Hydrolysis of the Chloro-substituted Acetyl Chlorides.*

By H. O. Pritchard and H. A. Skinner.

From measurements of the heats of hydrolysis of CH_3·COCl, CH_2Cl·COCl, $CHCl_2$·COCl, and CCl_3·COCl in aqueous-acetone solution, the following values (kcals. mole^{-1}) were obtained for the respective heats of formation (Q_f) of the liquids at room temperature: 66·2, 70·1, 68·7, and 68·8.

In an earlier communication, Carson and Skinner (*J.*, 1949, 936) reported some new measurements on the heats of hydrolysis of the acetyl halides. The present work is an extension of these studies to mono-, di-, and tri-chloroacetyl chlorides. Only one reference exists in the literature to previous measurements on the heats of hydrolysis of this group of compounds, in which Rivals (*Ann. Chim. Phys.*, 1897, **7**, 541) quoted values for the hydrolysis heats of mono- and tri-chloroacetyl chloride. The heat of hydrolysis of dichloroacetyl chloride does not seem to have been measured before.

Whereas acetyl chloride reacts very rapidly with water at room temperature, the chloro-substituted acetyl chlorides hydrolyse slowly, owing to their slow rate of dissolution in water. In aqueous acetone, on the other hand, the compounds hydrolyse quite rapidly, and we have found it convenient to use an aqueous acetone solvent in most of the present investigations.

Experimental.

Preparation of Compounds.—Chloroacetyl chloride was a B.D.H. product, purified by careful fractionation in a Fenske packed column; b. p. 105·4—105·5°/763 mm. The product was further purified by bulb-to-bulb distillation in a vacuum, and the pure fractions were collected and sealed in weighed glass ampoules.

Dichloroacetyl chloride was a B.D.H. product, purified in an exactly analogous manner; b. p. 107·0—107·4°/761 mm. The purified commercial sample was found on analysis to contain a small amount (0·03%) of sulphur (presumably from the thionyl chloride used in its preparation). As a check on the results obtained with the commercial sample, a further sample of dichloroacetyl chloride was prepared from dichloroacetic acid and benzoyl chloride (Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1326), and carefully purified by fractionation in a Fenske column operating at a high reflux ratio: b. p. 107·7—107·8°/767 mm.

Trichloroacetyl chloride was prepared according to Leimu's method (*Ber.*, 1937, **70**, 1040) by the action of thionyl chloride on trichloroacetic acid in benzene solution. The crude product was fractionated in a Fenske column, and later distilled *in vacuo* and sealed in weighed glass ampoules.

Calorimeter.—The reactions were carried out by breaking thin glass ampoules containing a known amount of the acid chloride into a large excess of water, or aqueous acetone. The reaction vessel was a silvered Dewar flask (1 l. capacity), with a single narrow neck (1½" diameter). The neck was closed with a polystyrene stopper which, in turn, was covered by a heavy close-fitting brass cap. A glass rotary propeller stirrer (100 r.p.m.) fitted centrally through the cap and stopper. Two additional holes through the stopper carried an electrical heater (for calibration purposes), and the resistance thermometer and leads. A circular brass plate, supported by two thin brass rods from the under side of the polystyrene stopper, served as a bottom bearing for the stirrer, and also for breaking the glass ampoules which could be depressed at any desired moment on to a cluster of spikes on one side of the plate. All the metal parts inside the calorimeter were rhodium-plated.

The Dewar vessel was submerged and supported in an accurately thermostated oil-bath, which, together with all the accompanying electrical apparatus, was kept in a thermostated room. The thermostat bath was a rectangular glass tank (15" × 12") fitted to a depth of 12" with white mineral oil. The bath was heated with mat heaters mounted about ½" off the bottom, and was efficiently stirred by a 10" four-bladed propeller driven by a flexible drive from outside the bath. The temperature control was maintained at 21° by a toluene regulator (extending through the bath). A Gouy head (Sligh, *J. Amer. Chem. Soc.*, 1920, **42**, 60) was used with the toluene regulator. The whole calorimeter assembly was essentially a modification of that used by Williams (*ibid.*, 1942, **64**, 1395).

The calibration heater was layer wound from 35 S.W.G. silk-covered Eureka wire on a 3-mm. ebonite rod to form an element 25 mm. in length (resistance 65 Ω). The heater was impregnated with cellulose acetate and encased in a platinum cylinder sealed to the end of a glass tube.

The resistance thermometer was a "Stantel" Thermistor (F 2311/300), and was carefully and rigidly mounted inside a thin glass tube, so that the tip was protected from external shock or pressure changes (Herington and Handley, *J. Sci. Instr.*, 1948, **25**, 434). Its resistance was measured to 0·05 Ω on a Cambridge glazed bridge in conjunction with a short-period reflecting galvanometer. The sensitivity of the resistance measurement is limited by the maximum continuous current rating of the thermistor: for the purpose of temperature measurement, this should not exceed 0·4 milliamp. The sensitivity under these conditions, with an optical lever of 1 metre, is *ca.* 1 Ω/cm.

Over small ranges of temperature, the temperature–resistance relation for a thermistor is of the form $T = k \log R$ (Becker, Green, and Pearson, *Trans. Amer. Inst. Elect. Eng.*, 1946, **65**, 711). By measuring the initial and final resistance of the thermistor (*i.e.*, R_1 and R_2) over the course of an experiment, the heat change (Q) can be obtained from $Q = K \log R_1/R_2$ where K is a constant that includes the water equivalent of the system and the thermistor constant k. The constant K can be determined by passing a measured amount of electrical energy through the calibration heater (*e.g.*, see McInnes and Braham,

J. Amer. Chem. Soc., 1917, **39**, 2110) so as to obtain a change in the thermistor resistance comparable with that observed in an average experiment.

In general, a resistance change of 50—60 Ω (corresponding to a temperature change of *ca.* 0·75°) was aimed at in each experiment, so that we were able to measure the temperature changes to an accuracy of the order of 0·002°. We have found that the thermistor element gives reproducible results over long periods of time, and can successfully replace a Beckmann thermometer or other more conventional temperature-recording instrument, provided that due care is exercised in keeping the element free from strain.

Heats of Hydrolysis.—The preliminary investigation were carried out on chloroacetyl chloride, which is representative of a number of acid chlorides that react slowly with water at room temperature. Ampoules containing about 3 g. of the acid chloride were broken under 750 c.c. of water. The hydrolysis required about 2 hours to reach completion. Since an accurate estimation of the heat leakages over such a long time period is difficult, we sought to attain a faster reaction by using an equivalent amount of sodium hydroxide solution as the hydrolysing agent (see Rivals, *loc. cit.*), but found no marked increase in the rate of hydrolysis by this change in solvent. However, by using aqueous acetone as the hydrolysis medium, the rate of reaction was much increased, and the reaction times were reduced to 10 minutes with a solvent medium of 150 c.c. of acetone in 600 c.c. of water. The heats of hydrolysis observed in this solvent ($Q_{obs.}$) are convertible into hydrolysis heats in a purely aqueous medium ($Q_{aq.}$) by making small corrections for the difference in the heats of solution of the reaction products in the two solvents. These solution heat corrections (amounting to about 1 kcal. mole^{-1}) were measured as required, the most important of them being the heats of solution of the chloroacetic acids, which are roughly 1 kcal. mole^{-1} *less* in the above aqueous acetone than in pure water, as shown below :

Acid.	Solvent (mole-ratio)	$Q_{solution}$ (kcal. mole^{-1}).
$CH_2Cl{\cdot}CO_2H$ (liq.)	$700H_2O$	+0·34
	($700H_2O$ + $35COMe_2$)	−0·42
$CH_2Cl{\cdot}CO_2H$ (crys.)	$1100H_2O$	−3·30
	($1100H_2O$ + $50COMe_2$)	−4·27
$CHCl_2{\cdot}CO_2H$ (liq.)	$1350H_2O$	+2·67
	($1350H_2O$ + $65COMe_2$)	+1·78
$CCl_3{\cdot}CO_2H$ (liq.)	$1700H_2O$	+2·55
	($1700H_2O$ + $80COMe_2$)	+1·70

Results.

Chloroacetyl Chloride.—The results obtained from five experiments on the hydrolysis of this chloride in *water* are given in Table I(*a*), and from six experiments in the aqueous acetone solvent in Table I(*b*). The calculated values for Q_f ($CH_2Cl{\cdot}COCl$, liq.) given in the final columns of these tables are derived from the equation :

$$Q_f(CH_2Cl{\cdot}COCl) = Q_f(HCl, aq.) + Q_f(CH_2Cl{\cdot}CO_2H, aq.) - Q_f(H_2O, liq.) - Q_{aq.}$$

where the symbol Q_f is used to denote the heat of formation from the elements in standard states. The values for Q_f(HCl, aq.), Q_f($CH_2Cl{\cdot}CO_2H$, aq.) and Q_f(H_2O, liq.) were taken from the "Selected Tables of Chemical Thermodynamic Constants" (National Bureau of Standards, Washington, U.S.A.). The values found for Q_f($CH_2Cl{\cdot}COCl$, liq.) in Tables I(*a*) and I(*b*) agree reasonably well with each other, due

TABLE I.

Heat of hydrolysis of $CH_2Cl{\cdot}COCl$.

Expt.	Reaction mixture.	Wt. R·COCl (g.).	R_1 (ohms).	R_f (ohms).	Q obs., kcals.	$Q_{aq.}$, kcals.	Q_f ($CH_2Cl{\cdot}COCl$, liq.), kcal. mole^{-1}.
	(a) *Hydrolysis in water.*						
1	R·COCl + $1300H_2O$	3·6086	1739·5	1678·6	—	22·56	69·91
2	R·COCl + $1520H_2O$	3·6950	1729·4	1677·6	—	22·44	70·04
3	R·COCl + $1590H_2O$	2·9464	1716·7	1669·3$_5$	—	22·59	69·89
4	R·COCl + $1470H_2O$	3·1982	1735·1	1681·0	—	22·62	69·86
5	R·COCl + $1510H_2O$	3·1155	1737·9	1684·9	—	22·71	69·77
					Mean values	22·59	69·89
	(b) *Hydrolysis in aqueous acetone.*						
1	R·COCl + ($1280H_2O$, $78COMe_2$)	2·9231	1707·8	1658·5	21·40	22·35	70·12
2	R·COCl + ($1190H_2O$, $72COMe_2$)	3·1746	1743·0	1690·6	21·42	22·37	70·10
3	R·COCl + ($1320H_2O$, $80COMe_2$)	2·8558	1743·5	1694·4	21·48	22·43	70·05
4	R·COCl + ($1220H_2O$, $74COMe_2$)	3·0843	1725·7	1672·6	21·34	22·30	70·17
5	R·COCl + ($1270H_2O$, $77COMe_2$)	2·9584	1742·7	1692·1	21·41	22·36	70·10
6	R·COCl + ($1630H_2O$, $98COMe_2$)	2·3058	1744·1	1704·9	21·35	22·30	70·19
					Mean values	21·40	22·35	70·12

allowance being made for the tardiness of the aqueous hydrolysis, and the possible small errors involved in the correction terms required by the aqueous-acetone hydrolysis.

Dichloroacetyl Chloride.—The hydrolysis of dichloroacetyl chloride was studied in the aqueous acetone mixture, in which solvent the rate of hydrolysis is rapid, requiring about 10 minutes. Results from 6 experiments are presented in Table II. The data therein were obtained with the purified commercial dichloroacetyl chloride. Some check experiments using a sample prepared by Brown's method (*loc. cit.*) gave virtually identical results; *e.g.*, two experiments gave $Q_{aq.} = 24{\cdot}84$ and $24{\cdot}83$ kcals.

Trichloroacetyl Chloride.—The hydrolysis of this chloride was similarly studied in the aqueous acetone solvent, and, as previously, reaction times of *ca.* 10 minutes were found. The results are given in Table III.

TABLE II.

Dichloroacetyl chloride in aqueous acetone.

Expt.	Reaction mixture.	Wt. R·COCl (gs.).	R_1 (ohms).	R_f (ohms).	$Q_{diss.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (kcals.).
1	R·COCl + (1150H_2O, 70$COMe_2$)	4·2658	1749·6	1684·8	24·80	25·67	68·78
2	R·COCl + (1380H_2O, 84$COMe_2$)	3·5678	1753·7	1699·1	24·85	25·72	68·75
3	R·COCl + (1240H_2O, 76$COMe_2$)	3·9763	1754·2	1693·7	24·74	25·61	68·86
4	R·COCl + (1240H_2O, 76$COMe_2$)	3·9815	1757·8	1696·5$_5$	24·97	25·84	68·63
5	R·COCl + (1255H_2O, 76$COMe_2$)	3·9272	1760·2$_5$	1700·0$_5$	24·84	25·71	68·76
6	R·COCl + (1265H_2O, 77$COMe_2$)	3·8989	1754·3	1694·5	24·93	25·80	68·68
				Mean values	24·86	25·73	68·74

TABLE III.

Trichloroacetyl chloride in aqueous acetone.

Expt.	Reaction mixture.	Wt. R·COCl (gs.).	R_1 (ohms).	R_f (ohms).	$Q_{diss.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (kcals.).
1	R·COCl + (1400H_2O, 85$COMe_2$)	4·3432	1754·7	1695·7	27·27	28·10	68·84
2	R·COCl + (1300H_2O, 79$COMe_2$)	4·6746	1754·6	1691·3	27·22	28·05	68·87
3	R·COCl + (1300H_2O, 79$COMe_2$)	4·6771	1754·9	1691·2	27·37	28·20	68·72
4	R·COCl + (1275H_2O, 78$COMe_2$)	4·7666	1755·9	1691·3	27·23	28·06	68·86
5	R·COCl + (1225H_2O, 75$COMe_2$)	4·9530	1754·4	1687·0	27·39	28·22	68·69
				Mean values	27·30	28·12	68·80

TABLE IV.

Expt.	Reaction mixture.	Wt. R·COCl (g.).	R_1 (ohms).	R_f (ohms).	$Q_{diss.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (kcals.).
	(a) *Acetyl chloride in water.*						
1	R·COCl + 1410H_2O	2·3207	1762·0	1705·8	—	22·17	66·15
2	R·COCl + 1380H_2O	2·3749	1760·6	1703·7	—	21·96	66·36
3	R·COCl + 1225H_2O	2·6734	1762·2	1697·3	—	22·28	66·03
4	R·COCl + 1290H_2O	2·5501	1762·4	1701·6	—	21·86	66·45
5	R·COCl + 1310H_2O	2·5025	1756·5	1696·4	—	22·09	66·22
6	R·COCl + 1280H_2O	2·5624	1747·4	1686·6	—	21·94	66·37
					Mean values	22·06	66·26
	(b) *Acetyl chloride in aqueous acetone.*						
1	R·COCl + (1060H_2O, 63$COMe_2$)	2·4652	1759·2	1698·3	21·34	22·08	66·22
2	R·COCl + (930H_2O, 57$COMe_2$)	2·8086	1757·5	1688·5	21·28	22·02	66·28
3	R·COCl + (1040H_2O, 63$COMe_2$)	2·5104	1758·5	1696·6	21·30	22·04	66·26
				Mean values	21·31	22·05	66·25

Acetyl Chloride.—As a check on the thermochemical method, we have remeasured the heat of hydrolysis of acetyl chloride, (*a*) in water and (*b*) in the aqueous-acetone solvent. As in the case of chloroacetyl chloride, the hydrolysis heat measured in the aqueous acetone ($Q_{diss.}$) was smaller than that measured in the purely aqueous solution ($Q_{aq.}$). After the necessary solution heat corrections had been made to $Q_{diss.}$, the derived $Q_{aq.}$ values agreed more or less exactly with one another. The results are summarised in Tables IV(*a*) and (IV(*b*). Compared with the results given earlier for acetyl chloride by Carson and Skinner (*loc. cit.*), there is a close correspondence in the observed heats of hydrolysis, but an apparent discrepancy in the values given for $Q_f(CH_3{\cdot}COCl, liq.)$. Part of the reason for this discrepancy lies in our use in this paper of the $Q_f(CH_3{\cdot}CO_2H, aq.)$ values recently recommended by the Bureau of Standards, Washington, but the main point of difference rests in an incorrect assumption by Carson and Skinner of a negligible heat of mixing of the aqueous hydrochloric and acetic acids in their experiments. We have since recalculated $Q_f(CH_3{\cdot}COCl, liq.)$ from the earlier data, making due allowance for the small mixing terms, and obtain $Q_f(CH_3{\cdot}COCl, liq.) = 66{\cdot}0 \pm 0{\cdot}20$ kcals. mole^{-1}. The agreement between the two sets of experimental data is thus seen to lie within the experimental error (*ca.* $\pm 0{\cdot}2$ kcal.) of the two investigations.

Discussion.

The results of the present investigation are summarised in the Q_f values listed below:

	Q_f (liq.) (kcals. mole^{-1}).	Q_f (gas) (kcals. mole^{-1}).	ΔQ_f.
$CH_3{\cdot}COCl$	66·2	59·4	+2·7
$CH_2Cl{\cdot}COCl$	70·1	62·1	−1·4
$CHCl_2{\cdot}COCl$	68·7	60·7	−0·2
$CCl_3{\cdot}COCl$	68·8	60·6	

The Q_f (gas) values are subject to some uncertainty, as data are not available for the heats of vaporisation ($\lambda_{vap.}$) of the chloroacetyl halides. We have estimated the $\lambda_{vap.}$ values by Trouton's rule, assuming the same value for Trouton's constant as obtains in acetyl chloride (Mathews and Fehlandt, *J. Amer. Chem. Soc.*, 1931, **53**, 3212), *viz.*, $\lambda_{vap.}$ ($CH_3{\cdot}COCl$) = 6·8 kcals. mole^{-1}.

The interesting feature of the above results lies in the *smallness* of the changes in Q_f arising from the successive replacement of each hydrogen atom in $CH_3{\cdot}COCl$ by chlorine atoms, and in the observed *fall* in Q_f in passing along the series $CH_2Cl{\cdot}COCl \longrightarrow CHCl_2{\cdot}COCl \longrightarrow CCl_3{\cdot}COCl$ (ΔQ_f values are negative). The increase in Q_f ($CH_2Cl{\cdot}COCl$) relative to Q_f ($CH_3{\cdot}COCl$) might be expected from analogy with other examples of chlorine substitution for which thermal data are available: *e.g.*,

	Q_f (kcals.).	ΔQ_f.		Q_f (kcals.).	ΔQ_f.
$CH_3{\cdot}CH_3$	20·2	+4·9	$CH_3{\cdot}CO_2H$ (liq.)	116·4	+3·2
$CH_2Cl{\cdot}CH_3$	25·1		$CH_2Cl{\cdot}CO_2H$ (liq.)	119·6	
$CH_2Cl{\cdot}CH_2Cl$	25·1	+6·1	CH_3	17·9	+1·7
$CH_2Cl{\cdot}CH_2Cl$	31·2		CH_2Cl	19·6	
$CH_2{\cdot}CH_2{\cdot}OH$	56·2	+3·9			
$CH_2Cl{\cdot}CH_2{\cdot}OH$	60·1				

On the other hand, the negative values of ΔQ_f in passing from $CH_2Cl{\cdot}COCl$ to $CHCl_2{\cdot}COCl$, and from $CHCl_2{\cdot}COCl$ to $CCl_3{\cdot}COCl$, are perhaps surprising. In the case of, *e.g.*, the chloroacetic acids, the ΔQ_f (liq.) values, although small, remain positive:

$CH_3{\cdot}CO_2H$ (liq.)	116·4	
		+3·2
$CH_2Cl{\cdot}CO_2H$ (liq.)	119·6	
		+0·6
$CHCl_2{\cdot}CO_2H$ (liq.)	120·2	
		+1·2
$CCl_3{\cdot}CO_2H$ (liq.)	121·4	

but it may be that a genuine negative trend in ΔQ_f is masked by using the Q_f (liq.) values in place of Q_f(gas). At present, the negative ΔQ_f's of the chloroacetyl chlorides are unique among the rather scanty thermochemical data on chloro-substituted compounds. It should be borne in mind, however, that the Q_f values of the chloroacetyl chlorides depend on the values we have accepted for the heats of formation of the chloroacetic acids.

There is some independent evidence that the substitution of a second and a third chlorine atom into a methyl group leads to a smaller increment in Q_f than that brought about the substitution of the first chlorine atom: *e.g.*,

$CH_3{\cdot}CH_3$	20·2	
		+4·9
$CH_3{\cdot}CH_2Cl$	25·1	
		+3·9
$CH_3{\cdot}CHCl_2$	29·0	

Recently, Lacher, McKinley, Walden, Lea, and Park (*J. Amer. Chem. Soc.*, 1949, **71**, 1334) have given values for the heats of chlorination of a number of fluoro- and fluoro-chloro-substituted ethylenes, including:

$$CH_2{:}CH_2 + Cl_2 \longrightarrow CH_2Cl{\cdot}CH_2Cl + 43{\cdot}60 \text{ kcals.}$$
$$CF_2{:}CF_2 + Cl_2 \longrightarrow CF_2Cl{\cdot}CF_2Cl + 57{\cdot}32 \text{ kcals.}$$
$$CF_2{:}CCl_2 + Cl_2 \longrightarrow CF_2Cl{\cdot}CCl_2 + 41{\cdot}08 \text{ kcals.}$$

The data suggest that the C–Cl bonds in the groupings $-CF_2-Cl$, $-CH_2-Cl$, and $-CCl_2-Cl$ are not equal in strength, but vary in the order $-CF_2-Cl > -CH_2-Cl > -CCl_2-Cl$. This is compatible with (but not proof of) decreasing ΔQ_f with increasing chlorine substitution on the same carbon atom.

Relatively little is known of the heats of formation of the chloro-acetaldehydes, which form an analogous group of compounds to the chloroacetyl chlorides. The increment in Q_f in passing from CH_3·CHO to CCl_3·CHO, is, however, quite small ($\Delta Q_f = 3{\cdot}3$ kcals.). The corresponding increment in the series of acetyl chlorides, *viz.*, 1·1 kcals., is smaller still, which might suggest that the replacement of −CHO by −CClO gives rise to a more powerful steric repulsion between the relatively bulky chlorine atoms of the groups CCl_3 and CClO, than exists between the groups CCl_3 and CHO. It would be useful to have further data, particularly on the bromo-acetyl halides, which should reveal steric repulsion effects in a more pronounced manner, if they indeed represent an important factor.

The authors express their thanks to Professor M. G. Evans for his interest in this work, and one of them (H. O. P.) to the Department of Scientific and Industrial Research for a maintenance allowance.

UNIVERSITY OF MANCHESTER. [*Received, October* 19*th*, 1949.]

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59. *The Dielectric Polarisation of Gaseous Sulphur Dioxide.*

By R. J. W. LE FÈVRE, I. G. ROSS, and B. M. SMYTHE.

Two sets of measurements for the above property, over the temperature range 290—440° K., have been obtained independently and with non-identical apparatus. The two apparatus both possess the simplicity of, but incorporate improvements upon, the oscillator–wavemeter combination used before by Le Fèvre and Russell.

The total polarisation of sulphur dioxide is represented in c.c. by ${}_gP = 10{\cdot}91 + 16164/T$, whence the dipole moment is 1·619 D., and the atomic polarisation *ca.* 1·4 c.c. (or 15% of the electronic polarisation).

THE work now to be described was undertaken for two reasons: (*a*) because sulphur dioxide, being one of the simplest substances having a negative Kerr constant, seemed an attractive case upon which to test various extant "rules" for the variation of apparent dipole moment with state (cf. Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374, and following paper), and (*b*) because a need was felt, during day-to-day observations of dielectric constant (ε) on gases, for a reference compound having a higher value of ε than that of carbon dioxide, the material previously used (*idem, loc. cit.*). The remainder of this communication deals with point (*b*).

Sulphur dioxide, being readily available and easy to handle and purify, was an obvious choice as the desired secondary standard. Its earlier examination by Jona (*Physikal. Z.*, 1919, **20**, 14) and Zahn (*Physical Rev.*, 1926, **27**, 455) suggested that it would have advantages over carbon dioxide in that, for it, $\varepsilon - 1$ is about nine times as great, at room temperature. Consequently the change of capacity (*i.e.*, the quantity actually measured) following the introduction of sulphur dioxide between the plates of a condenser would be ten times that produced by carbon dioxide under equivalent conditions. As calibrating materials, therefore, these two gases should lead to accuracies, other things being equal, in much the same ratio.

Our plan, accordingly, has been to make a careful comparison of sulphur dioxide with carbon dioxide, using for the latter the dielectric constant of 1·000905 at 25° and 760 mm. (corresponding to a temperature-invariant polarisation of 7·341 c.c.) adopted by Le Fèvre and Russell (*loc. cit.*).

APPARATUS.

Le Fèvre and Russell (*loc. cit.*) had incorporated the replaceable capacity (gas cell) into the circuit of a dynatron oscillator, the signal from which was picked up in an adjacent wavemeter. Very little of their original apparatus, however, being available in Sydney, it became necessary to rebuild *de novo*. Certain facts then emerged which caused us to discard the dynatron. Since this generator is still recommended in the second edition of "Dipole Moments" (Methuen, 1948) we wish to state briefly our reasons for the change. (*a*) The secondary emission from the plates of modern valves is less easy to induce than was the case with those commercially obtainable eleven years ago; we observed this empirically ourselves and later learned that changes in manufacture and design have been deliberately directed to this end (private communication from Messrs. Amalgamated Wireless, Australia Ltd.). (*b*) Supposedly identical valves can have secondary-emission characteristics which vary over wide limits. "Samples which are closely uniform when used as amplifiers display marked disparity in dynatron characteristics. The dynatron effect is more or less accidental, and consistency is not always sought for" (Scroggie, *Wireless Eng. and Expt. Wireless*, 1933, **10**, 527). (*c*) We found unexpectedly that the available inductance : capacity ratios were limited by the fact that oscillations ceased when $-L/CR$ was made less than $(R_s)_{\text{max.}}$ (R = resistance in the tank circuit, R_s = effective negative resistance of the valve, cf. Brunetti, *Proc. Inst. Radio Eng.*, 1937, **25**, 1595); the ast point was a serious drawback since

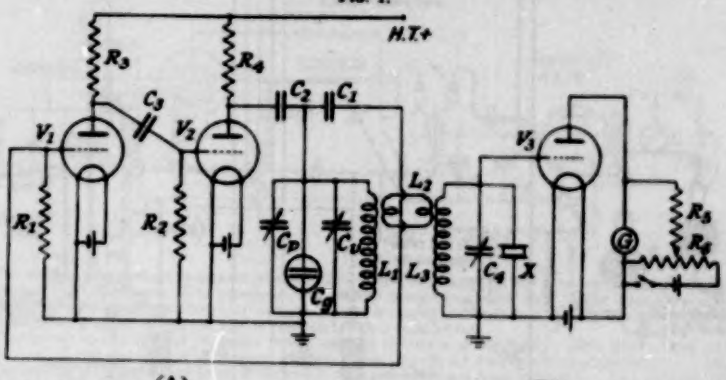
any factor tending to diminish the capacity of the gas cell would obviously react similarly upon the accuracy of our readings.

An experimental survey of other possible arrangements was therefore undertaken. These included variants of the heterodyne-beat method involving either audible or cathode-ray-tube reading-points. Several designs of oscillators were tried, mutually in pairs, or singly against the 50-c./s. mains or the carrier wave of a local Sydney broadcasting station. Finally we convinced ourselves that, except through a great increase of complexity (compare the circuit diagram of Stranathan, *Rev. Sci. Instr.*, 1934, **5**, 334) and of associated maintenance troubles, no significant improvement would be secured over the very simple equipment used by Le Fèvre and Russell. The problem was thus reduced to choosing a variable oscillator to replace the dynatron.

Eventually we adopted (*a*) a push–pull circuit of the Franklin type, and (*b*) a transconductance generator, both using power supplies drawn entirely from batteries. These, each with an attendant wavemeter containing a quartz resonator, have formed the basis of two apparatus, built and operated separately and independently (by I. G. R. and B. M. S. respectively). They will now be described *seriatim*.

Franklin Oscillator–Wavemeter Combination (*see Fig.* 1).—The lay-out comprises a Franklin oscillator *A* (cf. Witt and Franklin, B.P. 360,575) coupled to a wavemeter *B*. The specifications of the circuit components are as follows. Valves V_1, V_2, V_3: Radiotron 1H4-G. Capacitors: C_p, gas cell (described below); C_v, coarse variable condenser (second-grade Sullivan, maximum capacitance 200 pF.); C_p, precision variable condenser (see below); C_1 and C_2 should be equal and as small as possible, compatibly with adequate signal strength—7pF. was found to be satisfactory; C_3, 0·001 μF.; C_4, split-stator variable condenser, maximum capacitance 150 pF. Resistors: R_1, R_2, R_3, R_4, all 50,000 ohms; R_5, 20,000 ohms;

Fig. 1.



R_6, 1000-ohms potentiometer. Inductances: L_1, 90 turns 20 S.W.G. cotton-covered copper wire wound on a hexagonal bakelite former, 1½″ diameter, the whole coated with paraffin wax; L_2, 120 turns on a similar former; L_3, coupling coil, consisting of a single turn of stiff tinned copper wire, and located immediately above L_1, L_2, whose centres are 4½″ apart. *X*, quartz resonator crystal, frequency 1000 kc./s. (supplied in mount by Amalgamated Wireless, Australia, Ltd.); *G*, Cambridge galvanometer, sensitivity 1100 mm./microamp. at 1 m. The two circuits are built on separate steel chassis. C_p, C_v, and C_p are connected to the chassis by short lengths of coaxial cable.

Gas Cell.—The gas cell C_p resembles that described by Le Fèvre and Russell. Three coaxial rhodium-plated brass cylinders (16 gauge) are separated by small rectangular quartz spacers, 12 in all, the inner and outer cylinders (each 10 cm. long and earthed) being connected by a ring fitting tightly between them; the H.T. lead is led out, from the middle cylinder (9 cm. long), through a hole in the ring *via* a glass bush. The cell is sealed into an annular "Pyrex" glass cylindrical vessel, provided with a gas inlet. The leads are of 26 S.W.G. platinum wire, and penetrate the top of the vessel to the lower ends of mercury-filled glass tubes, into which dip the connections to the oscillator. The empty capacity is roughly 200 pF. The high-tension electrode is shielded by a brass foil wrapping (earthed).

The cell is located by a brass-rod scaffolding in an oil-thermostat. The temperature is read from a calibrated thermometer placed in a symmetrical position to the cell with respect to the heaters and stirrer. The electrical components, including batteries and excepting only the gas cell and precision condenser, are enclosed in a large heavily-lagged box, lined with sheet zinc (earthed) for shielding. No thermostatic control has been found necessary.

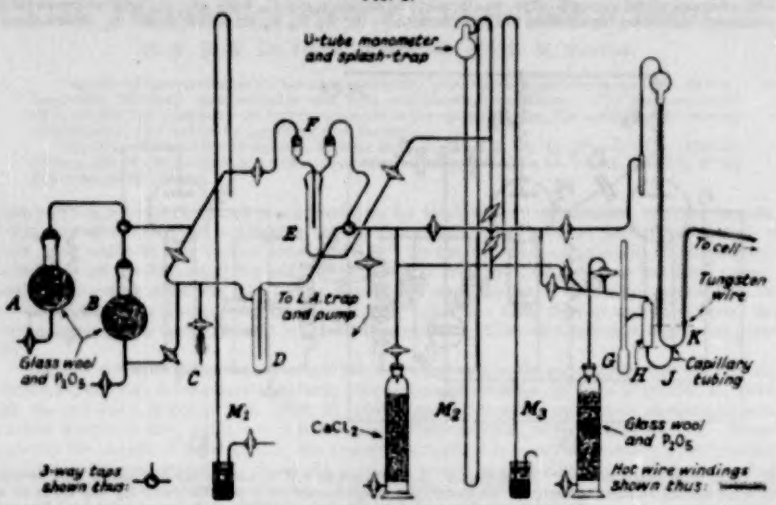
Precision Variable Condenser.—The design of the precision condenser is substantially the same as that shown in Fig. 4. The steps have diameters of 3 cm. and 2·45 cm., the cylinder around them is 20 cm. long and of 2·375 cm. inner radius. The working range is 8 pF. traversed in 160 turns; each division (1/100th turn) then corresponds to 0·0005 pF. The limit of reading (set by the response of *G*) is one-half of such a division. The total capacity is about 25 pF.

Performance of Oscillator.—The frequency stability of the oscillator was beyond expectations. After

it had run continuously for a fortnight, it was determined that, with C_2 at room temperature, under conditions in which a change of frequency of ½ c./s. could be detected, no change was observed during ½ hour.

Performance of this kind is remarkable. It would be of interest to obtain an explicit expression for the frequency in terms of all the circuit components, so that the probable influence of the more likely sources of frequency drift could be accounted for. However, the theoretical and practical aspects of this particular oscillator have been virtually neglected in the literature. An attempt to apply Kirchhoff's laws to the equivalent circuit of the oscillator, along the lines followed by Llewellyn (*Proc. Inst. Radio Eng.*, 1931, **19**, 2063) for several simpler oscillators leads to excessively involved expressions, which, in any event, must be regarded as only approximate in view of his tacit neglect of phase changes in the process of amplification (cf. Jen, *ibid.*, p. 2109). None the less, it seems clear that the chief reason for the observed stability is the small coupling, provided by the condensers C_1, C_3, between the tank and the rest of the circuit. The whole can be regarded as an LC circuit, the capacitative arm, C, of which is shunted by (*a*) one of the coupling condensers, C_1 or C_3, and (*b*) the other coupling condenser (C_1 and C_3 may be considered as approximately equal) in series with an impedance, Z, representing the remainder of the circuit. Then, to the extent that C_1 or C_3 is negligible compared with C (or $C + C_{1 \text{ or } 3}$) it is justifiable to take the impedance of this arm as that of C alone, *viz.*, $1/j\omega C$, which is not influenced by changes of Z.

FIG. 2.



Resonance Curve.—The form of the resonance curve is not that shown in the paper of Le Fèvre and Russell (*loc. cit.*). Because the coupling of the circuits exceeds the critical value, the curve has two humps, with two major crevasses (on either of which readings can be taken), and upwards of 30 minor crevasses, all excessively sharp and narrow, and too sensitive for use; these may be due to the excitation of subsidiary modes of vibration of the crystal.

The maximum anode current in the wavemeter is about 80 microamps. Since the galvanometer used gives its full deflection with about 1 microamp., a balacing e.m.f. is applied. The arrangement shown in Fig. 1 is one which, unlike a simple series arrangement of cell and rheostat, gives a uniform increase in back current as the knob of the potentiometer R_4 is turned.

Coaxial Cable Effect.—It has been mentioned that the condensers C_2, C_3, C_4 are connected to the chassis by coaxial cables. The important observation was made that the lengths of these cables influence strongly the amplitude of the resonance curve, as measured in the wavemeter circuit. In particular, if the length of cable connecting the cell (which constitutes the major part of the total capacity of the tank) to the rest of the circuit is doubled, the amplitude of the resonance curve is decreased by 30%. The effect of changing the lengths of cable to the smaller capacitances C_2 and C_4 is much less; while the connection of, say, one metre of unterminated cable in parallel with the other capacitances has no significant effect on the amplitude.

These considerations have a bearing on the design of the whole apparatus: to obtain maximum sensitivity it is necessary that the oscillator should be located as near as possible to the cell C_2.

It is not known whether they have been noted with other oscillators. Their explanation is difficult. The most obvious suggestion is that power dissipation in the cable causes the drop in signal strength; for as the capacitance across the end of the cable is increased, so also the admittance of the cable + capacitance as a whole increases, and consequently also the power dissipated. It is uncertain just how the amplitude

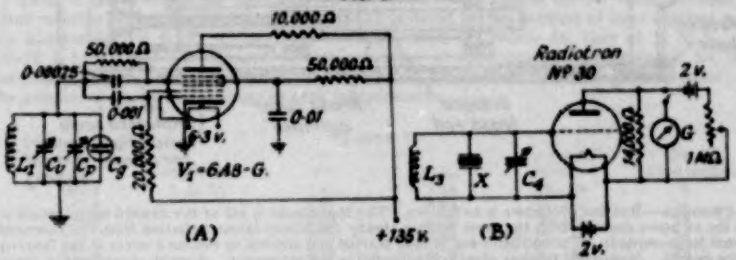
of oscillations depends on the effective resistance of the tuned circuit, although this is clearly a participating factor.

Significant losses in short lengths of high-quality cable are, however, unheard of. The cable used is A.W.A. Telcon h.f. cable, solid copper core (0·035" diam.), with braided outer conductor (0·25" diam.). The dielectric is a polythene–polyvinyl ester mixture, $\varepsilon = 2{\cdot}3$, resistivity 10^{17} ohm/cm., power factor 0·0003. The characteristic impedance, Z_0, is 70 ohms (modulus)—the calculated value is $75 + 1{\cdot}6j$ ohms—and the capacitance 21·5 pF./ft. The attenuation is 0·41 decibels/100 feet at 1 mc./s. (*i.e.*, for a correctly terminated line). Several different specimens of cable were used, and the connectors frequently refitted. The lengths of cable used (not more than 60 cm.) are no significant submultiple of a wavelength at 1 mc./s.

Using the appropriate exact transmission-line formulæ (Race and Larrick, *Trans. Amer. Inst. Elect. Eng.*, 1942, **61**, 526), the impedance of a cable of these specifications, 100 cm. in length, terminated by a capacitance of 500 pF., is found to be $1{\cdot}9 - 277j$ ohms, the real (resistive) part of which seems far too small to account for the effect described.

Gas-handling Apparatus.—The final form of the gas-handling apparatus is shown diagrammatically in Fig. 2. The bulbs, *A* and *B*, contain phosphoric oxide dispersed on glass wool, to serve for the preliminary drying of the gases. The connection of the traps (*E*, *D*) is such as to permit repeated cyclic distillation of gases. Of these traps, *E* is removable, and can thus be partly filled with drying agents, distillation over phosphoric oxide having been found the most effective method of drying. The bulbs, *F*, containing plugs of glass wool, serve to prevent phosphoric oxide being carried through the rest of the system when the liquid in the trap bumps while boiling. When blocked, the traps are cut out and replaced after washing.

FIG. 3.



The various connections to manometers enable a check to be kept on the pressures in all parts of the apparatus while distillation is in progress—a necessary precaution when icing of the downpipes of the traps occurs, with possible building up of back-pressures during distillation. M_2 is a U-tube manometer for working at positive pressures, and is equipped with a splash-trap.

The system to the right of M_1 is the device used by Groves and Sugden (*J.*, 1934, 1094; 1939, 1144, 1147). (Although not needed for sulphur dioxide, it was introduced during construction to allow higher-boiling liquids to be examined later, if desired.) The two gases are from cylinders. As a routine, they are dried (P_2O_5) and redistilled before admission to the cell.

Reading Procedure.—The oscillator and thermostat are allowed to run for about ½ hour to attain equilibrium. Two points on opposite sides of the bottom of the crevasse, about 14 condenser turns apart, and for which the galvanometer deflection is about 1 cm. per condenser scale-division, are used as reference points. Apart from the fact that during the taking of readings the heaters and stirrer in the thermostat are best switched off—since they cause slight instability—the sequence of operations is similar to that noted later (p. 280). Each set of readings takes approximately 12 minutes to perform.

Negative Transconductance Oscillator–Wavemeter Combination (*see Fig. 3*).—The oscillator (*A*) is built around a 6A8G Radiatron pentode, the three condensers C_V, C_P, and C_g being in parallel with the inductance L_1 (a ceramic grooved coil, 2" in diameter, wound with 54 turns of No. 20-gauge bare tinned wire). The variable condenser C_V is a short-wave radio commercial type of *ca.* 100 pF., used to set the frequency of the oscillator approximately to that of the quartz (so that the plate current of the wavemeter is on the crevasse, and fine tuning then possible with the precision condenser C_P). C_g remains unaltered during a series of measurements. Resistors and other capacities are specified on Fig. 3. The wavemeter (*B*) is mounted on the same chassis as the oscillator, and the whole, with associated power supplies, housed in an insulated box to maintain fairly constant ambient temperatures around the components and to prevent radiation from the heated thermostat standing alongside.

Gas Cell.—This is simpler than that used by I.G.R., consisting of two brass tubes 9·5 cm. long, the inner of which (diameter, 5·1 cm.) is mounted concentrically with the outer (diameter 5·4 cm.). Six "Pyrex"-bead spaces, inserted under slight tension, prevent movement of the two cylinders. The assembly is sealed into an annular "Pyrex" envelope with the same kind of electrical connections as for the cell previously described. The outside cylinder is earthed. The empty capacity of this cell is approx. 80 pF.

The cell-mounting, thermostat, and gas supply arrangements are substantially the same as those of I.G.R. above.

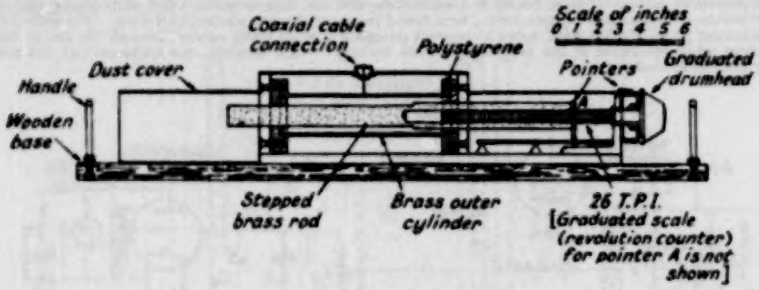
The Precision Condenser, C_P.—Details of this are shown as Fig. 4. It, as also that of I.G.R., utilises a "stepped-rod" on the principle described by Watson, Rao, and Ramaswamy (*Proc. Roy. Soc.*, 1934, **143**,

556), but with an altered design to provide a more rigid method of support of the high-potential component. Two polystyrene rings are grooved tightly to hold the brass cylinder, A (internal diameter 4·7 cm., length 20 cm.), and screwed to the ¼" steel end-plates. Insulation by polystyrene is as efficient as the method used by Watson and obviously permits robust overall construction. The stepped brass rod (diameters, 3·0 and 2·68 cm.) is precision-turned to slide through two graphite-lubricated bearings (B) on the steel end-plates. The steel screw on which the stepped rod rotates has a pitch of 26 turns per in. and is ground true with the threaded sleeve of the rod. The total capacity of the condenser is ca. 30—40 pF. and the variable range 4 pF.

A moving pointer slides against a linear scale, indicating numbers of turns, while the rotating head (marked in hundredths) gives fractions of turns; readings are always taken in the same direction to avoid errors due to backlash. Each condenser shows satisfactory "straight-line" properties, confirmed by the fact that readings of capacity differences for a particular pressure of carbon dioxide at the same temperature are the same at any point on the scale. In practice most readings are taken over the middle of the scale because of possible end-effects.

FIG. 4.

Precision variable condenser.



Operation.—Routine procedure is as follows. The thermostat is set at the desired temperature and left for 12 hours during which the room reaches steady conditions (some radiation from the thermostat cannot be prevented). The oscillator etc. is then started and allowed to run for 5 hours at the frequency of the quartz. Meanwhile sulphur dioxide is collected in the apparatus. A series of readings at varying pressures (generally 12—16 pressures at a particular temperature, requiring some 2—3 hours) may now be taken. With the cell evacuated, the precision condenser is adjusted until zero current flows through the galvanometer. A second reading is obtained such that some 6—8 turns of the condenser are needed to pass from the first point on the current–capacity crevasse to that which is exactly opposite. This range provides the greatest sensitivity and stability. Next, the vapour is introduced into the cell, after 3 minutes the pressure is recorded, and capacity readings are taken as before. The cell is lastly evacuated, and after 3 minutes a final set of readings made. These timings are important if the mean of the two vacuum readings is to be the "true" vacuum reading corresponding to the vapour reading. This is so, since a slow drift in frequency cannot be entirely avoided. Providing, however, this is regular over 9 minutes (the period between two vacuum readings) it need not impair the measurements.

RESULTS.

The results are recorded as described by Le Fèvre and Russell (*loc. cit.*; see p. 378 for a sample set). The method used in a relative one, requiring preknowledge only of the polarisation of the standard gas (carbon dioxide in the present work). In what follows δC is the difference between drum and scale readings of the precision variable condenser when the cell is filled to a measured pressure, and the mean of the two "vacuum" readings taken before and after that particular "vapour" reading; p is the pressure in cm.

Values of $\delta C/p$ for each temperature are first plotted against pressure. A curved graph at this stage would suggest deviations from ideality of the gas, and/or to surface adsorption (Zahn, *Physical Rev.*, 1926, **27**, 329); however, in the case of carbon dioxide no such deviation occurs. We therefore take as the limiting value of $\delta C/p$ at zero pressure the arithmetic mean of the observed $\delta C/p$ readings.

Evidently the compressibility of carbon dioxide may be ignored. The measurement of pressure is actually used as an indirect measurement of the density of the gas, the underlying assumption being that δC (which is proportional to the change in dielectric constant) should be proportional to the number of molecules present per c.c., *i.e.*, to the density. For an ideal gas the density is proportional to the pressure, and $\delta C = k.p$. For a real gas we must substitute for p, the observed pressure, the "ideal pressure," p_i, that it would exert if Boyle's law were

observed, *i.e.*, $\delta C = k.p_1 = kp/(1 - Ap)$, where A is the compressibility; hence $\delta C/p = k/(1 - Ap)$.

This is a non-linear relation. Yet in the case of carbon dioxide, a linear graph, parallel to the p axis, is obtained. One can conclude therefore that for this substance compressibility considerations are unimportant. Direct experiments (Cawood and Patterson, *J.*, **1932**, 2180; cf. Moles, Toral, and Escribano, *Trans. Faraday Soc.*, **1930**, **25**, 1439) have shown very low A values, *e.g.*, 0·0053 at 21°, 0·0048 at 31° (where p is measured in *metres* of mercury). From these, even at room temperatures, the correction to $\delta C/p$ would amount only to $+\frac{1}{2}\%$ at 50 cm.

With sulphur dioxide below 100° the graphs *are* curved. They were accordingly extrapolated graphically to zero pressure, when, as may be seen from the equation above, $p = p_1$ and $\delta C/p = \delta C/p_1$. (For sulphur dioxide the compressibilities are 0·0165 at 30°, 0·0132 at 50°, corresponding in the first instance to a correction of $+8\%$ at 50 cm.) This extrapolation covers effects due to association of the molecules, which for sulphur dioxide is responsible for part of the compressibility. Garulla and Perez (*Z. physikal. Chem.*, **1944**, **193**, *A*, 162) find, from measurements of thermal conductivity, the equilibrium constant for the dissociation of the double molecule $(SO_2)_2$ to be given by $\log K_p = -8200/4{\cdot}573T + 8{\cdot}70$. At 40° and 1 atmosphere the partial pressure of $(SO_2)_2$ is thus only 1·14 cm., or 1·5% of the total pressure. This contribution tends, of course, to zero at $p \longrightarrow 0$.

Table I refers to carbon dioxide. To the "observed" figures in the third column the linear relation between $x' = (\delta C/p)_{p \to 0}$ and $1/T$ is fitted by the method of least squares. For the apparatus of I. G. R. we have $x' = 0{\cdot}3308 + 2083{\cdot}6/T$, while for that of B. M. S., $x' = 0{\cdot}0413 + 1408{\cdot}1/T$. The fourth column contains x' appropriately recalculated for each temperature. Also recorded are the pressure ranges, over which the readings were taken, and the number of observations made at each temperature.

TABLE I.

T (°K.).	Apparatus.	x'.	$x'_{calc.}$	p range in cm.	No. of observations.
291·4	I. G. R.	7·47	7·48	15—69	9
317·8	,,	6·91	6·89	20—66	16
349·0	,,	6·38	6·30	20—93	13
375·1	,,	5·75	5·89	21—67	10
437·5	,,	5·14	5·10	21—66	18
289·3	B. M. S.	4·92	4·91	20—71	9
314·5	,,	4·51	4·52	23—73	12
351·2	,,	4·07	4·06	39—71	9
357·3	,,	3·99	3·98	22—76	14
373·0	,,	3·77	3·82	21—61	5
401·5	,,	3·60	3·55	39—70	10
429·0	,,	3·31	3·32	56—74	9
456·5	,,	3·13	3·14	37—75	10

TABLE II.

Polarisation of sulphur dioxide.

T(° K.).	Apparatus.	ε.	P.	$P_{calc.}$	$P_{calc.}$	p range in cm.	No. of observations.
297·2	I. G. R.	65·2	65·99	65·86	65·30	13—66	15
340·1	,,	56·7	58·36	58·99	58·43	23—53	8
349·0	,,	4·86	57·32	57·76	57·22	20—65	10
351·0	,,	4·80	56·92	57·50	56·96	20—65	17
381·4	,,	4·19	53·74	53·82	53·29	20—67	11
408·5	,,	3·73	51·04	51·00	50·48	20—65	11
(437·0	,,	3·17	46·27	48·41	47·89	20—66	18)
296·2	B. M. S.	42·5	65·10	65·26	65·48	19—66	9
308·2	,,	40·0	63·22	63·48	63·70	19—69	11
307·2	,,	39·9	63·39	63·29	63·51	20—62	6
343·5	,,	32·9	58·27	57·75	57·96	30—63	7
382·5	,,	26·9	53·10	52·95	53·16	20—71	8
406·5	,,	24·0	50·27	50·46	50·67	21—65	13
440·5	,,	20·9	47·34	47·39	47·60	24—70	12
444·0	,,	20·6	47·02	47·10	47·31	24—71	18

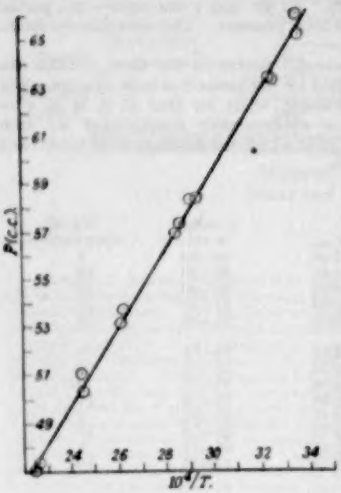
To evaluate the polarisation of sulphur dioxide, from parallel sets of measurements on this gas, we note that at zero pressure (where $\varepsilon + 2 = 3$) the Clausius–Mosotti expression becomes

$P = K(\delta C/\rho)_{p\to 0}(pv)_{p\to 0}$, where v is the volume occupied by one mole of gas. But in this limit $(pv)_{p\to 0} = p_0 v_0$ (in the nomenclature above) $= v$, the molar volume of a perfect gas at one atmosphere. This is a general relation for all gases, K being a constant throughout. Therefore, if we put $(\delta C/\rho)_{p\to 0}$ for carbon dioxide $= x'$, and for sulphur dioxide $= x$, then $P_{SO_2} = P_{CO_2}.x/x' = 7{\cdot}341\ x/x'$ c.c. (using the polarisation of carbon dioxide given at the beginning of this paper).

The values thus determined for P_{SO_2} are plotted against $1/T$, and straight lines again fitted by the method of least squares. The results are shown in Table II.

Fig. 5 shows the observed polarisations (column 4 of Table II) superimposed on the graph of $P = 10{\cdot}91 + 16164/T$ (column 6 of Table II). Column 5 of Table II gives the polarisations calculated from each set of data separately by the equations: $P = 11{\cdot}31 + 16213/T$ (I. G. R.) and $P = 10{\cdot}72 + 16155/T$ (B. M. S.). The incomplete agreement seems to be connected more with the shape and layout of components than with the manner in which the apparatus is operated. Relative performance may be examined by the scatter of $\delta C/\rho$ for a particular gas at a given temperature. In the above determinations the estimated order of accuracy is about $\pm 1\%$ for carbon dioxide. For sulphur dioxide, with $\delta C/\rho$ about nine times as great, the corresponding figure is *ca.* $\pm 0{\cdot}2\%$, not $\pm 0{\cdot}1\%$ as might be expected. The loss of accuracy is due probably to slight imperfections in the precision condensers, which necessarily have a very slight longitudinal play (to enable screw action to take place at all), quite apart from any deviations from linearity in capacitance, and to actual mechanical changes occasioned by rotating their drumheads upwards of 50 times between vacuum and gas readings.

FIG. 5.



The expressions just written for P should be compared with $10{\cdot}64 + 16100/T$, computed by us from data recorded by Zahn (*Physical Rev.*, 1926, **27**, 455). Earlier papers by Badeker, Klemenčic, and Verain (references and summaries in "International Critical Tables," Vol. VI, p. 74) give dielectric-constant estimations at too few set temperatures and pressures to permite valuation of the constants A and B in the Debye equation. Jona (*Physikal Z.*, 1919, **20**, 14), however, reports fuller figures; from these we calculate [using $(\varepsilon - 1)/(\varepsilon + 2)$, and least squares]: $P = 20218/T - 0{\cdot}194$. A negative A term is, of course, impossible and must be attributed to experimental errors, which A reflects sensitively.

The Dipole Moment of Sulphur Dioxide.—This, from $\mu = 0{\cdot}01273B^{\frac{1}{2}}$, is, for the various B values already given, 1·619 D. ($B = 16164$), 1·620 D. ($B = 16213$), 1·618 D. ($B = 16155$), and 1·615 D. ($B = 16100$; Zahn), 1·81 D. ($B = 20218$; Jona).

The Faraday Society Table of dipole moments (Appendix to *Trans.*, 1934, **30**) shows, under sulphur dioxide, a reference to Braunmühl, whose paper does not however include this substance. It further quoted Jona's result as $\mu = 1{\cdot}76$ D., but this appears to have been obtained using $P = V(\varepsilon - 1)/3$. We have given special consideration to the experiments of Jona, since, in contrast with the estimates (1·615—1·619) by Zahn and us, his datum resembles the higher group (1·7—1·9 D.) drawn from observations of electrostriction (Frivold, *Physikal. Z.*, 1921, **22**, 603; Kliefoth, *Z. Physik*, 1926, **39**, 402). This phenomenon, however, does not yet rest upon a proven theoretical basis, and the measurements involved (changes in volume of *ca.* 3×10^{-4} c.c.) are very delicate. Frivold, in three determinations between 292·0° and 292·8°, found $\mu = 1{\cdot}74$, 1·90, and 1·86 D. High field strengths, E, being employed, Kliefoth questioned the sufficiency of the simple (Gans) relation, used by Frivold, namely: $\delta v/v_0 = E^2(\varepsilon - 1)/8\pi p$, and considered the effect of higher powers of E. It is significant that his estimate for μ_{SO_2} is 1·7 D.—*i.e.*, lower than Frivold's.

Jona was among the first to use a heterodyne-beat H.F. method but during the 30 years since his publication there has been great improvement in radio components and practice. His

figure, moreover, may be offset by lower ones, calculable by the refractivity method from the single ($\varepsilon - 1$) measurements of other earlier workers: 1·61 D. from Klemenčic (*Sitzungsber. Akad. Wiss. Wien*, 1885, II, **91**, 712); 1·60 D. from Bädeker (*Z. physikal. Chem.*, 1901, **38**, 305); 1·59 D. from Verain (*Ann. Physique*, 1914, **1**, 255).

For the above reasons, and noting the near agreement between Zahn and ourselves, we record the dipole moment of sulphur dioxide as 1·619 D.

Atomic Polarisation of Sulphur Dioxide.—The refractive index of this gas has been measured by, *inter alia*, Cuthbertson and Cuthbertson (*Proc. Roy. Soc.*, 1909, *A*, **83**, 171) and Huxley and Lowery (*ibid.*, 1943, *A*, **182**, 207). The last-named authors have reviewed the subject and reported an extended study of the dispersion. From their Sellmeier formula: $(n - 1)_0 = 5{\cdot}220 \times 10^{27}/(8178 \times 10^{27} - \nu^2)$ we estimate n^2_∞ to be 1·001277, and (V_0 being 22·4141, *vide* International Critical Tables, Vol. 3, p. 3) R_∞ to be 9·54 c.c. A corresponding computation from the Cuthbertson data yields 9·58 c.c. These are close to the $[R_L]_D$ of 9·49 c.c. found by Nasini (*Gazzetta*, 1883, **13**, 296). The A value (cf. p. 282) cannot be more certain than $10{\cdot}9 \pm 0{\cdot}6$, so that ${}_AP = 1{\cdot}4 \pm 0{\cdot}6$ c.c., *i.e.*, from 1 to 3% of the total polarisation at room temperatures or 8—21% of ${}_EP$ (for comparison, the analogous % for carbon dioxide is 12; Watson and Ramaswamy, *Proc. Roy. Soc.*, 1936, *A*, **156**, 144). We have attempted its *a priori* calculation, following Coop and Sutton (*J.*, 1938, 1280). Wagner (*Z. physikal. Chem.*, 1943, *A*, **193**, 55), from Raman spectra, gives the O–S–O angle as 135° and the O–O force constant as $1{\cdot}217 \times 10^5$ dynes/cm. If $r_{S-O} = 1{\cdot}43 \times 10^{-8}$ cm. (Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1940, **62**, 1270), $f_{\text{bending}} = V_0 = 2{\cdot}49 \times 10^{-11}$ ergs/radian; or, with $r_{S-O} = 1{\cdot}37 \times 10^{-8}$ cm. (Sponer, "Molekülspektren," Springer, 1935), $V_0 = 2{\cdot}28 \times 10^{-11}$ ergs/radian (we note that the corresponding figure for ozone is $2{\cdot}34 \times 10^{-11}$, *i.e.*, of the same order; Simpson, *Trans. Faraday Soc.*, 1945, **41**, 215). For the apical angle quoted, μ_{S-O} is 2·12 D.; for one of *ca.* 120° (as earlier reported by Dadieu and Kohlrausch, *Physikal. Z.*, 1932, **33**, 165) it is 1·62 D. Coop and Sutton (*loc. cit.*; cf. Bloom and Sutton, *J.*, 1941, 727) give ${}_AP = 4\pi n N\mu_1{}^2/9V_0$, where n is the number of angular co-ordinates necessary to express completely the possible independent modes of bending of the opposing dipoles, each of magnitude μ_1. Sutton's actual cases (*e.g.*, *p*-benzoquinone) all had high degrees of symmetry. Dekker (*Rec. Trav. chim.*, 1945, **64**, 126) has applied Sutton's equation to triangular molecules by using $\mu_1 \sin(\alpha/2)$ instead of μ_1 (2α = angle between valency bonds). For sulphur dioxide he estimates ${}_AP$ as 0·07 c.c. This seems unnecessarily small, for from the figures given above we find the lowest ${}_AP$ to be 0·13 c.c., and the highest 0·28 c.c. Nevertheless, the observed quantity is much larger. The computation is sensitive to 2α. Thus, using the lower r_{S-O} and V_0 values, for $2\alpha = 120°$, 135°, 140°, 150°, 155°, and 160°, atomic polarisations follow of respectively 0·15, 0·28, 0·37, 0·68, 1·00, and 1·56 c.c.

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60. *Sulphur Dioxide. Its Apparent Dipole Moment as a Solute and as a Pure Liquid compared with the True Value as a Gas.*

By R. J. W. LE FÈVRE and I. G. ROSS.

Measurements at 25°, and calculations by the Debye–Clausius–Mosotti formulæ, provide moments of 1·6$_1$ D. (in benzene), 1·6$_2$ D. (in carbon tetrachloride), *ca.* 1·4 D. (in chloroform), and 1·1$_4$ D. (as pure liquid).

Sulphur dioxide is the simplest molecule with a negative Kerr constant whose apparent dipole moments as liquid, or in solution, have been compared with the true value (*i.e.*, 1·6$_4$ D., see preceding paper) as measured in the gaseous state.

The ratios found for $\mu_{\text{sln.}} : \mu_{\text{gas}}$ or $\mu_{\text{soln.}} : \mu_{\text{gas}}$ disagree with forecasts based on various previous formulæ or "rules" for the effects of media on μ_{apparent}. Theories utilising the conception of hindered molecular rotation in liquid systems are also unsatisfactory in their present forms. A recent treatment of the $\mu_{\text{soln.}} : \mu_{\text{gas}}$ aspect of the problem by Ross and Sack, however requires a small *diminution* in μ_{apparent} on dissolution in benzene or carbon tetrachloride. The experimental indications are that the direction of change is as predicted.

For the purpose indicated in paragraph (a) of the opening of the previous paper, we required dielectric polarisation data for sulphur dioxide, both as a pure liquid, and as a solute in a non-polar solvent. The literature, however, contained only a few ε and d points for the former

state, and none for the latter. We have therefore made appropriate measurements on sulphur dioxide–benzene and sulphur dioxide–carbon tetrachloride systems. These are now recorded, together with the details of our redetermination of ε_{SO_2}.

Solutions of Sulphur Dioxide.—These were made up by dissolving the gas in a weighed amount of solvent and observing the increase of weight.

For benzene, in which sulphur dioxide is extremely soluble, the solution was prepared by attaching the flask to the outlet tube *C* of the gas apparatus (see Fig. 3, preceding paper), and controlling the vaporisation of purified liquid sulphur dioxide so as to maintain a gas pressure of about 1½ atmospheres. The flask was cooled to *ca.* 5° and shaken occasionally, absorption taking place readily, about 2 hours sufficing to make up a solution of adequate concentration. By not passing the gas *through* the liquids the possibility of solvent loss (which would result in an underestimate of the weight fraction) was avoided.

For carbon tetrachloride, with which this process would have been tedious, owing to the lower solubility, a small quantity of liquid sulphur dioxide was collected in a test tube attached to the ground glass cone on *C*. When the gas pressure had reached atmospheric, the tube was detached and the contents introduced into the weighed benzene, the flask being closed with a rubber stopper, and reweighed.

The *density* measurements were made with a Sprengel pyknometer of about 10 ml. capacity, with capillary side-arms. The liquid was moved by pressure of dry air, rather than by suction, which caused liberation of gas. Even so, evolution of vapour did occur at times during adjustment in the thermostat, and the accuracy of the measurements, while adequate, is less than that made with non-volatile solutes. The *dielectric constant* determinations were made with the resonance apparatus described by Calderbank and Le Fèvre (*J.*, 1948, 1949). The cell was filled and emptied by air pressure. The results are given in Table I, the symbols being those customarily used by us (cf. *J.*, 1937, 1805).

TABLE I.

Sulphur dioxide in benzene.						Sulphur dioxide in carbon tetrachloride.		
10^4w_1.	$(d_{12})^{25}_4$.	$(\varepsilon_{12})^{25}$.	β.	$\alpha\varepsilon_2$.	$_TP_1$.*	10^4w_1.	$(\varepsilon_{12})^{25}$.	$\alpha\varepsilon_2$.
0	0·87378	2·2725	—	—	—	0	2·2261	—
14396	0·87821	2·3508	0·351	—	—	7438	2·2805	7·32
29537	0·88179	2·3853	0·354	4·35	58·8	7834	2·2835	7·29
34459	0·88462	2·4241	0·360	4·40	64·6	8972	2·2884	6·95
40972	0·88690	2·4515	0·366	4·37	63·8	12178	2·3127	7·11
59644	0·89252	2·5409	0·360	4·50	64·1	24634	2·3994	7·04
73010	0·89705	2·6117	0·364	4·61	64·6	31909	2·4354	6·58

* Calculated by Sugden's equation (*Trans. Faraday Soc.*, 1934, **30**, 720).

From the above data for benzene as solvent the dipole moment can be evaluated: mean $\beta = 0{\cdot}358_5$, $\alpha\varepsilon_2 = 4{\cdot}21 + 5{\cdot}20w_1$ whence $_TP_\infty = 64{\cdot}72$ c.c., and—since the distortion polarisation = 10·9, c.c. (*cf.* preceding paper)—$\mu = 1{\cdot}61_5$.

With carbon tetrachloride as solvent, our density determinations produced somewhat scattered values (−0·21 to −0·32) for β. Recourse was therefore made, as a check, to the careful dilatometric measurements of Horiuchi (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1931, **17**, 126) on solutions of gases in certain organic liquids. Extrapolation to zero concentration of Horiuchi's figures for the coefficient of dilatation, δ, of sulphur dioxide in carbon tetrachloride gives $\delta = 2{\cdot}435 \times 10^{-3}$. If the density of sulphur dioxide at N.T.P. is taken as 2·9269 g./l. (International Critical Tables, Vol. **3**, p. 3), the limiting rate of decrease in density with concentration of sulphur dioxide can be calculated; whence $\beta = -0{\cdot}318$. (A similar calculation with benzene, taking $\delta = 2{\cdot}138 \times 10^{-3}$, gave $\beta = +0{\cdot}363$, in good agreement with our direct measurements in this medium.) We note that the densities of the two weakest sulphur dioxide–carbon tetrachloride solutions (11—16%) used by Adams and Rogers (*J. Amer. Chem. Soc.*, 1939, **61**, 112) correspond to a β of −0·22. Nevertheless, since both $1 - \beta$ and $\alpha\varepsilon_2$ increase with dilution, we have taken −0·318 and 7·32 respectively (whence $_TP_\infty = 65{\cdot}15$ c.c. and $\mu = 1{\cdot}61_5$ D.) to provide a maximum estimate of the apparent moment.

Six solutions of sulphur dioxide in chloroform were also examined but were marred by unavoidable escapes of gas. The approximate values obtained for β and $\alpha\varepsilon_2$ were −0·11 (±0·01) and 8·4 (±0·25) respectively; from these, μ is *ca.* 1·4 D.

Liquid Sulphur Dioxide.—A number of measurements of the dielectric constant of this material are on record. Coolidge (*Wied. Annalen*, 1899, **69**, 125), using Drude's second method (*ibid.*, 1897, **61**, 466), found $\varepsilon = 13{\cdot}75$ at 14—15° (frequency 300 mc./s.). Schlundt (*J. Physical Chem.*, 1901, **5**, 157, 403), with the same method, gave $\varepsilon = 12{\cdot}35$ at 22°, while Verain (*Ann. Physique*, 1914, **1**, 523) obtained values about half those reported by previous workers. Everscheim (*Ann. Physik*, 1902, **8**, 539) used a bridge method, and covered the temperature range from 114° to 157·5°, just above the critical temperature. His results can be summarised (when $0° < t° < 150°$) by the relation: $\varepsilon_t = 15{\cdot}6 - 0{\cdot}078t$. Using Everscheim's temperature coefficient of ε, we may reduce these readings to a single temperature (0°) for comparison: 14·9 (Coolidge), 15·5 (Schlundt), 14·6 (Everscheim).

Coolidge and Schlundt, and presumably also Everscheim (although this is not explicit in his paper), used for calibration various benzene–acetone mixtures, whose dielectric constants had been measured by Drude (*loc. cit.*). In our experience pure acetone is a most difficulty reproducible substance for use as a standard, and, in this connection, we would emphasise that the value quoted by Drude for $\varepsilon_{\text{benzene}}$ at 19° (2·260) is markedly less than the value (2·2846) given by Hartshorn and Oliver (*Proc. Roy. Soc.*, 1929, *A*, **123**, 664).

Having found that the overall capacity of his cell, empty, did not vary measurably with temperature (a likely result if the effect of changes in cell dimensions due to expansion of the condenser and glass container are analysed), Everscheim used throughout the whole temperature range the value of the replaceable cell capacitance as measured at one temperature. His measurements are therefore probably all in error by a constant factor, depending on the calibration of his cell and the purity of his material.

We have accordingly re-measured the dielectric constant of sulphur dioxide at 0° (when the vapour pressure is only 1·53 atm.) and used the (corrected) slope of Everscheim's graph to calculate the value of 25° (vapour pressure, 3·82 atm.). By working at the lower temperature, the system could be closed with ordinary taps, instead of sealing off the inlet tubes, thus considerably lessening the chance of disturbing the cell and leads between readings.

To this end, a cell was used, consisting of two coaxial brass tubes, $\frac{1}{4}$" and $\frac{3}{8}$" external diameter, and 13 mm. (inner) and 15 mm. long respectively, spaced by four glass beads (diameter *ca.* 1 mm.), fitting into shallow sockets on the inner cylinder. The assembly hung rigidly from two stout tungsten wires which passed through the glass ("Pyrex") into mercury-filled cups, whence leads were taken to a coaxial cable connector, fixed on the wooden bridge locating the cell in a constant temperature bath. The latter was a lagged 3-l. beaker, filled with ice and water and provided with a levelling device. Adequate stirring, it was found, could be achieved by dropping a few small fragments of solid carbon dioxide into the bath.

The capacitance measurements were performed with an apparatus similar to that used for measuring the dielectric constants of sulphur dioxide solutions.

The cell was calibrated at 0°, using five liquids whose dielectric constants had been determined at this temperature by Le Fèvre (*Trans. Faraday Soc.*, 1938, **34**, 1127), together with ethylene dichloride.

It was found that for any given liquid, the value of $(C_{\text{obs}} - C_{\text{air}})$ was reproducible to better than two scale divisions of the variable condenser connected in parallel with the cell, a liquid with $\varepsilon - 1 = 2$ giving a difference of approx. 200 such divisions.

The results of this calibration are given in Table II, the cell constant being the replaceable capacitance, measured in divisions of the condenser scale.

TABLE II.

Calibration of liquid cell.

Liquid.	$(C_{\text{obs}} - C_{\text{air}})$.	$\varepsilon - 1$.	Cell constant.
Carbon tetrachloride	131	1·2734	102·9
Toluene	144	1·4350	100·3
Ether	379	3·803	99·7
Chloroform	433	4·169	103·5
Ethyl bromide	933·5	9·19	102·0
Ethylene dichloride	1038·5	10·314	103·5

Acetone ($\varepsilon - 1 = 20·58$) was also used, but with it the resonance curve was damped and widened. Rejecting the ether reading as improbably low, and noticing that any error in the cell constant calculated from toluene is magnified by the fact of its having a small dielectric constant, we adopted the mean value of 103 for the cell constant, with a probable error of about $\pm 1\%$. We are not justified in assuming any deviation from linearity of $(C_{\text{obs}} - C_{\text{air}})$ with dielectric constant.

The value taken for the dielectric constant of ethylene dichloride needs further comment, in view of the recently published value (extrapolated to 0°) of 11·77 (Clay, Dekker, and Hemelryk, *Physica*, 1943, **10**, 768). The figure used in Table II is that found by Davies (*Phil. Mag.*, 1936, [vii], **21**, 1008), whose objective was to establish this liquid as a standard substance. Davies has reviewed determinations prior to his own; most of those which are subsequent, despite their claimed accuracy of 0·02%, are not supported by details of any practical re-examination of the problem of obtaining reproducibly purified specimens. The earlier figure, due to Davies, has accordingly been retained.

Sulphur dioxide, from a cylinder, was dried by repeated fractional distillation over phosphoric oxide, the gas being passed each time through phosphoric oxide–glass wool bulbs. It was finally distilled from fresh phosphoric oxide directly into the cell, which for the purpose was connected *via* its right-hand arm to the outlet tube *C* of the gas-handling apparatus (Fig. 3, preceding paper) by thick-walled rubber tubing, the system being made vacuum tight. When surrounded by alcohol at about −80°, the cell took 1—2 hours to fill. This accomplished, the alcohol was replaced by ice-water, and the capacitance measured when stationary conditions had been attained. The sulphur dioxide was then cautiously allowed to boil off, air (dried by passage over 5 feet of P_4O_{10}) passed through for about a minute, and the "air" reading taken. The differences, $C_{\text{obs}} - C_{\text{air}}$, so obtained were constant at 1450·0, whence $\varepsilon_{SO_2} = 15·0_4$ at 0°, and (using the corrected $\delta\varepsilon/\delta t$ of −0·075) 13·20 at 25°.

From these quantities the "apparent" dipole moments according to the formulæ of Debye, ${}_0P = M[(\varepsilon - 1)/(\varepsilon + 2) - (n^2 - 1)/(n^2 + 2)]/d$, and Onsager, ${}_0P = M(\varepsilon - n^2)(2\varepsilon + n^2)/d\varepsilon(n^2 + 2)^2$, can now be calculated approximately. The refractive index, n, of sulphur dioxide for the D line at 20° is 1·342 (Nasini, *Gazzetta*, 1883, **18**, 296) corresponding approximately to 1·362 at 0° (Bleekrode, *Proc. Roy. Soc.*, 1884, **37**, *A*, 339). Nasini (*loc. cit.*), Cailletet and Matthias (*Compt. rend.*, 1887, **104**, 1564), Lange (*Z. angew. Chem.*, 1899, **12**, 277), Stowe (*J. Amer. Chem. Soc.*, 1929, **51**, 410), Seyer and Peck (*ibid.*, 1930, **52**, 14), and Eversole, Wagner, and Bailey (*J. Physical Chem.*, 1941, **45**, 1388), quote densities for liquid sulphur dioxide which, after conversion to 0° and 25°, provide the average values 1·435 (0°) and 1·369 (25°).

By substitution, we find:

		0°.	25°.
Debye equation	$_0P$	27·0 c.c.	27·3 c.c.
	μ	1·10 D.	1·16 D.
Onsager equation	$_0P$	84·4 c.c.	79·4 c.c.
	μ	1·93 D.	1·96 D.

For large values of ϵ, the Debye expression is highly insensitive to small variations in this quantity. With regard to the Onsager equation, it can easily be shown that for ϵ *ca.* 15, n^2 *ca.* 2, $\Delta_0P/_0P = -0{\cdot}87\ (\Delta n^2/n^2) = 1{\cdot}34\ (\Delta\epsilon/\epsilon) = -\Delta d/d$, and that it will therefore be affected chiefly by errors in ϵ. These we estimate generously at $\pm 1\%$, whence the uncertainty in $_0P$ is $\pm 1{\cdot}2$ c.c., and in μ, $\pm 0{\cdot}07$ D.

Discussion.—As a preliminary, the foregoing experimental results (as calculated by the Debye equation) are summarised in convenient form as Table III.

TABLE III.

State.	Gas.	Solution in C_6H_6.	Solution in CCl_4.	Solution in $CHCl_3$.	Liquid.
$_0P_{\text{observed}}$	65·15	64·7$_3$	65·1$_4$ †	51·2	38·2
$n^2_{\text{observed}}/n^2_{\text{calc}}$	—	0·99$_3$	1·00 †	0·74	0·50
$\delta\mu^2/\mu_{\text{gas}}$	—	−0·00$_4$	0 †	−0·136	−0·28

* $\delta\mu = \mu_{\text{liquid}}$ or $\mu_{\text{soln.}}$ minus μ_{gas}. † A maximum estimate, cf. p. 284.

Solutions of Sulphur Dioxide.—The particular relevance of sulphur dioxide as a substance for the investigation of solvent effects lies in the fact that it is a relatively simple molecule of shape not greatly different from ellipsoidal, and possessing a negative Kerr constant (K at 760 mm. for light of 5400 A. $= -9{\cdot}4 \times 10^{-15}$; Stuart and Volkmann, *Ann. Physik.*, 1933, **18**, 140). It is thus well suited for testing the rule—first devised by Goss (*Trans. Faraday Soc.*, 1934, **30**, 751) on the basis of the Raman–Krishnan theory (*Proc. Roy. Soc.*, 1928, *A*, **117**, 589) of the dielectric constant of anisotropic liquids (as applied to liquid mixtures) and subsequently advanced by Higasi (*Sci. Papers Inst. Phys. Chem. Res. Toyko*, 1936, **28**, 284) from a different viewpoint—that the sign of the solvent effect should be opposite to that of the Kerr constant of the substance. This rule was dependent upon the consideration of spheroidal molecules, or of those which could be regarded as approximately spheroids; recently, however, Ross and Sack (*Proc. Physical Soc.*, in the press), by widening the Raman–Krishnan and Higasi arguments to ellipsoidal molecules with *three unequal* axes, have shown that even on the basis of these—themselves not complete treatments—the Kerr constant rule could not have had a completely general applicability; indeed for molecules in which the resultant moment is parallel to the mid-axis of its ellipsoidal approximation—and sulphur dioxide is one such—the sign and magnitude of the Kerr constant need give no indication at all of the sign and magnitude of the solvent effect.

By extending Onsager's approach (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) to the static dielectric constant of liquids and solutions (again, the original was derived for spherical molecules only) to ellipsoidal molecules of uniform polarisability, Ross and Sack obtain a new expression for the solvent effect, in which the sign of $\delta\mu$ depends not only on the shape of the solute molecule but also on its refractive index and on the dielectric constant of the solvent medium. We merely note here, quoting from their paper, and applying their calculation also to the carbon tetrachloride solution, that while the generalised Higasi theory, even in an amended form [which tends to reduce $\delta\mu/\mu$ by a factor of $(\epsilon + 2)/3\epsilon$], requires a $\delta\mu/\mu = +0{\cdot}011$ in both benzene and carbon tetrachloride, the Ross–Sack equation leads to $\delta\mu/\mu = -0{\cdot}016$ (in benzene) and $-0{\cdot}012$ (in carbon tetrachloride). Thus, while it is not correct quantitatively, the new equation is qualitatively so in successfully covering the small decrease in apparent moment, noted (cf. Table III) with the former solvent, and inferred for the latter.

We conclude therefore, from both the theoretical considerations of Ross and Sack and the experimental evidence presented here for sulphur dioxide, that values of the Kerr constant can no longer be regarded as a satisfactory basis for predictions concerning the solvent effect.

Liquid Sulphur Dioxide.—It is now generally recognised that the assumptions made in the derivation of the Debye equation are too drastic to allow it to be used to calculate the dipole moments of molecules from measurements of the pure liquid substances; the data in the last column of Table III concerning liquid sulphur dioxide illustrate this.

Onsager's expression (cf. p. 285) for spherical isotropic molecules has been found to be of more general applicability. It has been critically tested on 31 pure liquids by Böttcher

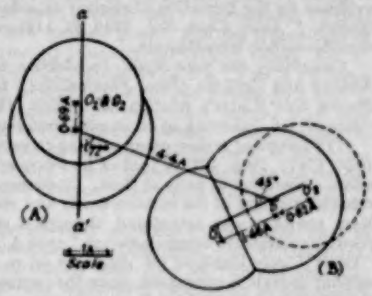
(*Physica*, 1939, **6**, 59), who finds it to give values of $\mu_{apparent}$ in good accord with μ_{gas}. Wilson (*Chem. Reviews*, 1939, **25**, 377), however, has pointed out that in view of Onsager's neglect of association effects and of molecular anisotropy, this agreement is probably fortuitous. He also suggests that instead of using for n the extrapolated value of the refractive index at infinite wave-length, the effective refractive index, defined by: $(n^2_{eff} - 1)/(n^2_{eff} + 2) = 4\pi N\alpha/3 = d({}_EP + {}_AP)/M$ should be taken, where $({}_EP + {}_AP)$ is the observed distortion polarisation (preferably from gas measurements).

Wilson has adapted Onsager's theory to cover the anisotropy of the molecular units forming a liquid: if n_2 is the effective refractive index corresponding to the polarisability α_2 along the dipole axis (defined by an equation similar to that just written), and if n is the average effective refractive index, then $M(\varepsilon - n^2)/d\varepsilon(2\varepsilon + n^2) = 4\pi N\mu^2 (n_2^2 + 2)^2/9kT(2\varepsilon + n_2^2)^2$ and n_2 can be estimated from Kerr constant–polarisability data. The results of these several calculations applied to sulphur dioxide at 25° are as follows:

Data used: ${}_EP + {}_AP = 10{\cdot}9$; $d = 1{\cdot}369$, $\varepsilon = 13{\cdot}20$, $n^2_{eff} = 1{\cdot}911$, $n_2^2 = 1{\cdot}769$.
Onsager's equation (using n^2_{eff}): ${}_OP_{liq.} = 74{\cdot}07$. ${}_OP_{liq.}/{}_OP_{gas} = 1{\cdot}365$.
Wilson's equation: ${}_OP_{liq.} = 78{\cdot}31$. ${}_OP_{liq.}/{}_OP_{gas} = 1{\cdot}444$.
Kirkwood's equation (see below); $g = 1{\cdot}399$.

It will be observed that Onsager's equation (even when n^2_{eff} is used in place of n^2), as well as Wilson's extension of it, lead to predicted values of the orientation polarisation approximately 40% too high.

An explanation of the increased apparent moment of sulphur dioxide in the liquid state, as indicated by these equations, may be found in the results of an *X*-ray examination of liquid sulphur dioxide at room temperature by Bastiansen and Finbak (*Tids. Kjemi Bergvesen Met.*, 1945, **4**, 2). Their figures for the shape of the sulphur dioxide molecule in the condensed phase agree exactly with the figures of Pauling and Brockway (*J. Amer. Chem. Soc.*, 1935, **57**, 2684) for the gas. They give also intermolecular distances and angles which describe a quasi-crystalline structure with 4-fold (tetrahedral) co-ordination of sulphur dioxide molecules about a central molecule. Unfortunately, these authors do not show the relative disposition of any two complete adjacent molecules, but we may determine this by applying the reasonable principle that, of the four molecules *B*, *C*, *D*, and *E*, surrounding a central molecule *A*, two, say *B* and *C*, must be disposed with respect to *A*, as is *A* with respect to *D* and *E*, since *A* is one of the four molecules adjacent to each of the latter. Then it is found that on the figures of Bastiansen and Finbak only one type of mutual orientation is possible. This is shown in the figure; the dotted O atom is the one whose position we infer; it lies either above or below the plane of the figure; the two O atoms of the central sulphur dioxide molecule *A* lie in the plane through *aa'* perpendicular to the plane of the figure. A second molecule *B* can occupy the positions similar to those of *B* on the other side of *aa'*, and *D* and *E*, the locations of whose S atoms only are given by Bastiansen and Finbak, are in front of and behind, respectively, and above, *A*, disposed in the same way as *A* is to *B*. If we calculate the field due to each of the four dipolar molecules at *A* (assuming the intervening dielectric to be uniform, *i.e.*, no refraction of the lines of force) it is found that in each case there is a component parallel to and in the same sense as the dipole of *A*; the components perpendicular to this will cancel on the average, in view of the choice of positions available for each of *B*, *C*, *D*, *E*. Thus there is a polarising field producing an additional moment which, combined vectorially with the original moment, must increase it; to attempt to calculate precisely this short-range dipolar action would involve too many assumptions, but the general conclusion, that it will reinforce rather than detract from the original moment, still holds.



Finally, Onsager's equation has been further modified by Kirkwood (*J. Chem. Physics*, 1939, **7**, 911; *Ann. N.Y. Acad. Sci.*, 1940, **40**, 315), who has allowed, in principle, for a mutual action of any kind between the molecules, although—since this action cannot yet be evaluated in precise terms—the equation he derives is not amenable to direct test. Kirkwood finds $M(\varepsilon - 1)(2\varepsilon + 1)/9\varepsilon d = {}_EP + {}_AP + 4\pi N\mu\bar{\mu}/9kT = {}_EP + {}_AP + 4\pi N\mu^2 g/9kT$. Here μ is the

dipole moment of the molecule in the absence of an applied field, and is evaluated sufficiently accurately by the relation due to Onsager (*loc. cit.*): $\mu = \frac{2\varepsilon + 1}{2\varepsilon + n^2} \cdot \frac{n^2 + 2}{3} \cdot \mu_0$; $\bar{\mu}$ is the total moment of a molecule and its neighbours in the region surrounding it, in which the local dielectric constant differs effectively from the overall macroscopic value.

The "correlation parameter," g, is a measure of the degree and strength of association of the molecules in the liquid. For water and alcohols, which have strong intermolecular hydrogen bonding, Oster and Kirwood (*J. Chem. Physics*, 1943, **11**, 175) have attempted to evaluate g theoretically (but even then on questionable assumptions; Frenkel, "Kinetic Theory of Liquids," Oxford, 1946). For sulphur dioxide, which has no such strong bonding, this is not possible.

However, g is accessible from experimental data, and the value obtained (see above) shows that sulphur dioxide falls in the same class as liquids such as ammonia, ether, acetone, and nitrobenzene, for all of which g is in the range 1·1 to 1·7; we conclude therefore that sulphur dioxide shows especially marked association.

In this connection we would mention that the extraordinary mutual solubility of benzene and sulphur dioxide (amounting to complete miscibilty of two substances which are chemically dissimilar) might lead to a suspicion that some sort of association of a more formal kind than the type so far considered may exist in these mixtures, although the freezing-point curve gives no indication of this. Seyer and Peck (*J. Amer. Chem. Soc.*, 1930, **52**, 14), from determinations of the Eötvös constant, inferred that sulphur dioxide was associated only below 0°, and not noticeably so in mixtures. In harmony with this, we find the total polarisations (cf. Table I, p. 284) to be substantially independent of concentration. There seems, therefore, to be no evidence for the formation of sulphur dioxide–benzene complexes. Viscosity data (Adams and Rogers, *J. Amer. Chem. Soc.*, 1930, **61**, 112) suggest a similar conclusion for the system sulphur dioxide–carbon tetrachloride.

Concerning the pure liquid, in addition to the remarks of Seyer and Peck, we note that Awbery and Griffiths (*Proc. Physical Soc.*, 1936, **48**, 372) report sulphur dioxide as obeying Herzog and Kudar's relation (*Z. Physik*, 1933, **80**, 217) between latent heat of fusion and viscosity, *i.e.*, behaving as an unassociated liquid.

The foregoing review offers nothing to support the discussion of Le Fèvre and Le Fèvre (*J.*, 1935, 1747; 1936, 487) or that of Le Fèvre and Russell (*J.*, 1936, 491), both of which assumed solute association in pairs at least. Statements made in the second 1936 paper require amendment in the light of the measurements now recorded for sulphur dioxide. Thus the sign of the Kerr constant was introduced through a structural coincidence, molecules for which K is positive or negative being classed as "type A" or "type B" respectively. Further, both these "types" were idealised (cf. diagrams on p. 1784 of the 1935 ref.) beyond usefulness where sulphur dioxide is concerned, since the mutual orientation of the sulphur dioxide molecules in the liquid, as indicated by X-ray evidence and supported by apparent moment determinations, corresponds in no way to the type of association postulated for molecules of type B, which, it was put forward, should pack together collinearly, with their dipoles parallel and in line. In particular, the predictions made by Le Fèvre and Russell (second 1936 ref. above) for cases where a solute and solvent are each of B type, are shown to be incorrect by the present findings for sulphur dioxide in chloroform and in itself.

Theories Involving Hindered Rotation in Liquids.—A number of other attempts have been made to introduce features of the structure of liquids into discussions of their dielectric properties. Stewart's idea of cybotaxis (*Rev. Mod. Physics*, 1930, **2**, 116; *Physical Rev.*, 1931, ii, **37**, 9), and the experimental evidence behind it, seem particularly suggestive, in that the predisposition of a liquid to contain more or less ordered arrangements over small elements of its volume springs from the anisotropic properties of the molecules concerned. Debye (*Physikal. Z.*, 1935, **36**, 100, 193; *Chem. Reviews*, 1936, **19**, 171) and Fowler (*Proc. Roy. Soc.*, 1935, *A*, **149**, 1) have assumed that dipolar molecules in liquids are not free to rotate but only to execute oscillations about axes whose directions change slowly, but over short periods of time are fixed by the fields of the neighbouring molecules. Thus Debye writes for the orientation polarisation: ${}_0P = (4\pi N\mu^2/9kT)[1 - L^2(\beta)]$, where $L(\beta)$ is Langevin's function of $\beta = E/kT$. For sulphur dioxide we have ${}_0P_{\text{liq.}}/{}_0P_{\text{gas}} = 0{\cdot}5 = [1 - L^2(\beta)]$, whence E, the "binding energy" $= 3{\cdot}4kT$; for comparison, water shows ${}_0P_{\text{liq.}}/{}_0P_{\text{gas}} = 0{\cdot}193$ and $E = 11kT$, and ammonia, 0·41 and 4·4kT respectively. The theoretical calculation of E has not yet been accomplished. Attempts, using the molecular interactions obtained by London (*Trans. Faraday Soc.*, 1937, **33**, 8) in conjunction with inter-dipole distances of $2r$, where $r^3 = 0{\cdot}916 \times$ molecular volume $\times 10^{-24}$,

yield only $E = 0{\cdot}25kT$ for water and $0{\cdot}1kT$ for ammonia. A more serious objection is that the factor $[1 - L^2(\beta)]$ fails to deal with cases (*e.g.*, trimethylamine) where ${}_0P_{liq.}/{}_0P_{gas}$ exceeds unity.

Kincaid and Eyring (*J. Chem. Physics*, 1938, **6**, 620) have approached the problem *via* the "free volumes" and the "free angle ratios" (f.a.r.) of molecules in a condensed phase. Both these concepts, to a first approximation, concern the regions in which displacement can occur. For molecules with three degrees of freedom the f.a.r. is written δ_3 and the rotation taken as restricted between the limits of the polar angles 0 and θ_1, then $\mu^2_{liq.}/\mu^2_{gas} = 1 - [(1 + \cos\theta_1)/2]^2$. Since it is often approximately true that the potential curves for the rotation of the molecule about the three axes are symmetrical, $\delta_3 = \delta_1^{3/2}$ and $\delta_1 = (1 - \cos\theta_1)/2$. For the angular water molecule, $1/\delta_3$ is calculable from the product $(6{\cdot}1 \times 10^{-120})$ of the principal moments of inertia and various constants as $10{\cdot}14 \times 10^{60} \times (ABC)^{\frac{1}{2}} = 25{\cdot}05$; δ_3 therefore is 0·116, whence $\mu^2_{liq.}/\mu^2_{gas} = {}_0P_{liq.}/{}_0P_{gas} = 0{\cdot}22$, *i.e.*, of the order found by direct measurement (0·19). A parallel calculation cannot yet be made for sulphur dioxide ($ABC = 13{\cdot}9 \times 83{\cdot}2 \times 97{\cdot}1 \times 10^{-120}$, Mulliken, *Rev. Mod. Physics*, 1942, **14**, 204) since the frequencies associated with hindered translation or rotation do not seem to have been observed (cf. Cartwright, *Nature*, 1935, **136**, 181; *Physical Rev.*, 1936, **49**, 470; Strong and Woo, *ibid.*, 1932, **42**, 267; for the Einstein functions in the water case just cited we have used $\nu = 170$ and 500 cm.$^{-1}$ from Hibben, "The Raman Effect and its Chemical Applications," Reinhold, 1939, p. 320).

The required $(\delta_3)_{SO_2}$ has therefore been estimated from the product $\delta_3 V_f (= RT/p \cdot \exp \Delta H_{vap.}/RT$; Kincaid and Eyring, *loc. cit.*) and the equation: $(v_f)^{1/3} = 2RTV^{vw}/N^{vw}\Delta E_{vap.}$ (Glasstone, Laidler, and Eyring, "Theory of Rate Processes," McGraw-Hill, 1941, p. 479), in which the symbols have conventional meanings or are defined in the sources cited; $T = 298°$; p, the vapour pressure of liquid sulphur dioxide at 298°, is 3·863 atm. (International Critical Tables, Vol. III, p. 236), the molecular volume, 46·8 (present paper), and the latent heat of evaporation 345 joules/g. (estimated from data given by International Critical Tables, Vol. V, p. 138). Thus $\delta_3 = 0{\cdot}03$ and $\delta_2 = 0{\cdot}097$, whence $\mu^2_{liq.}/\mu^2_{gas}$ should be *ca.* 0·2. This is 2·5 times too small. From the observed ratio, δ_3 is seen to be 0·29. Kincaid and Eyring note that δ_3 from dielectric constant measurements tends to exceed $(\delta_3)^{3/2}$ from other sources (*e.g.*, with methanol, $\delta_3 = 0{\cdot}25$ from ϵ methods and 0·13 by the alternative routes). Nevertheless the theory evidently fits the simple molecule sulphur dioxide too inadequately for it to merit the status of a general *a priori* explanation of solvent effects. In its present form it has the further disadvantage that it cannot forecast correctly those circumstances which lead to ${}_0P_{liq.}/{}_0P_{gas}$ ratios greater than one.

Concluding Remarks.—We have disregarded certain early empirical relationships, such as those proposed by Müller, Jenkins, Arkel and Snoek, Sugden, Henriquez, etc. (cf. Glasstone, *Ann. Reports*, 1936, **33**, 117 for summary and references) since they all required the ratio $\mu_{liq.\ or\ soln.}/\mu_{gas}$ to be less than unity—a forecast already adequately established as not always correct (*e.g.*, Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374; compare paraldehyde, following paper). The present work on sulphur dioxide has now demonstrated the inapplicability of a number of other treatments which have hitherto shown signs of sufficiency. The Ross–Sack theory alone remains with promise of explaining apparent moment ratios in dilute solutions. Even it will not cover pure polar liquids. Perhaps it is impracticable to hope for a "universal formula" in the latter problem. Indeed, as knowledge of liquid "structures" accumulates, the need for such a "formula" will decline, since the calculations necessary should then require only the ordinary considerations of electrostatics.

Materials not Specified Previously.—Carbon tetrachloride. Technical carbon tetrachloride was refluxed over mercury for 16 hours, then shaken for some hours successively with concentrated sulphuric acid, dilute sodium hydroxide solution, and water. After storage over calcium chloride for a week, it was fractionally distilled from paraffin wax, again dried (P_2O_5) for further week, redistilled, left over phosphoric oxide for 3 weeks, and distilled immediately before use, the middle half of the distillate (b. p. 76·7°) only being collected.

Toluene. Commercial toluene was shaken several times with small quantities of concentrated sulphuric acid and washed with dilute aqueous sodium hydroxide and distilled water; it was then dried ($CaCl_2$), refluxed for some hours over mercury, dried (P_2O_5) for a week, and redistilled; b. p. 110·6°.

Ether. To remove the chief impurities present in "B.P." ether, it was shaken with $\frac{1}{10}$th of its volume of 10% silver nitrate solution (cf. Werner, *Analyst*, 1933, **58**, 335), washed with water, concentrated sulphuric acid, and water, dried (Na wire), fractionally distilled, dried, and again distilled; b. p. 34·6°.

Chloroform. An "AnalaR" supply was successively shaken with sodium hydrogen sulphite solution, water (twice), concentrated sulphuric acid (3 times) and water, dried ($CaCl_2$) for 3 weeks, distilled, dried (P_2O_5), and redistilled, b. p. 61·2°.

Ethyl bromide. Ethyl bromide (from B.D.H.) was shaken successively with concentrated sulphuric acid, sodium carbonate solution, and water (each 4 times, and for some hours). It was then dried

($CaCl_2$), fractionally distilled, dried (P_2O_5), distilled again, and stored over phosphoric oxide, being distilled before use; b. p. 38·4°.

Ethylene dichloride. The commercial liquid was washed with dilute potassium hydroxide solution and water, dried ($CaCl_2$), distilled, and twice dried (over P_2O_5), and redistilled; b. p. 83·5°.

Acetone. This was shaken with a small quantity of 15% silver nitrate, to which had been added an equal volume of N-sodium hydroxide (Werner, *loc. cit.*). It was then dried (K_2CO_3), distilled, set aside over potassium carbonate, and redistilled before use. This specimen was still sufficiently moist to damp the oscillations appreciably; a further rapid distillation over phosphoric oxide failed to bring about an adequate improvement; b. p. 56·3°.

Benzene. "AnalaR" thiophen-free benzene was dried over sodium wire, purified twice by fractional crystallisation, and stored over sodium wire.

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61. *The Dielectric Polarisations of Liquid, Dissolved, and Gaseous Paraldehyde.*

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New measurements now recorded show paraldehyde to have a larger apparent moment in the liquid (1·7$_9$ D.) or dissolved states (light petroleum, 1·7$_7$; dioxan, 1·9$_5$; carbon tetrachloride, 1·9$_4$; benzene, 1·8$_7$; chloroform, 2·1$_0$) than as a gas (1·44). The last datum follows from the equation: $_2P = 44{\cdot}47 + 12792/T$. The ratios $\mu_{liq.}/\mu_{gas}$ or $\mu_{soln.}/\mu_{gas}$ are the greatest yet recorded.

These results are discussed in relation to extant theories for the role of the medium in dipole moment measurements.

The atomic polarisation of paraldehyde is approximately one-third of the electronic.

THE present communication extends an earlier one by Le Fèvre and Russell (*J.*, 1936, 496), in which paraldehyde was examined merely because it had a large negative Kerr constant. During the intervening thirteen years, however, its molecular dimensions have been established (Ackerman and Mayer, *J. Chem. Physics*, 1936, **4**, 377; Brockway and Carpenter, *J. Amer. Chem. Soc.*, 1936, **58**, 1270; Gerding *et al.*, *Rec. Trav. chim.*, 1939, **58**, 604, 615; 1941, **60**, 258). Its shape allows it credibly to be fitted within an ellipsoid of rotation about the resultant dipole moment as axis (cf. Calderbank and Le Fèvre, *J.*, 1949, 199). Paraldehyde becomes accordingly an attractive "model" upon which to test extant theories for the variation of apparent polarisation and state.

Le Fèvre and Russell (*loc. cit.*) recorded dielectric constant and density figures for the pure liquid and solution of it in nine solvents, but fearing the presence of the equilibrium, $C_6H_{12}O_3 \rightleftharpoons 3CH_3{\cdot}CHO$, refrained from proceeding to a discussion. It is now clear that this anxiety was unjustified, since in ordinary organic media depolymerisation becomes marked only in the presence of acid catalysts (Orton and McKie, *J.*, 1917, **109**, 185; Bell, Lidwell, and Vaughan-Jackson, *ibid.*, 1936, 1792). Moreover, in 1936 the necessary polarisation data for the gaseous state were lacking; the provision of these, together with a number of recent or repeated results in various solvents, is the main object of this paper.

The total molecular polarisation of paraldehyde vapour as a function of the absolute temperature has been found to follow the equation: P (c.c.) $= 44{\cdot}47 + 12792/T$, whence $\mu = 1{\cdot}44$ D., and the electronic and atomic contributions together (44·47 c.c.) are seen to exceed the $[R_L]_D$ value (33·1 c.c.) used by Le Fèvre and Russell.

Further, where dissolved paraldehyde is concerned, our additional determination in benzene, light petroleum, and dioxan make it evident that rectilinear relationships do not hold between concentration (as weight fraction, w_1) and either the dielectric constants (ε_{12}) or the densities (d_{12}) of the mixtures (compare Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). With trioxymethylene and trithioformaldehyde, signs of the same phenomenon were found by Calderbank and Le Fèvre (*J.*, 1949, 199). Accordingly both our new measurements in non-polar solvents and those from Le Fèvre and Russell (relating to carbon tetrachloride and chloroform) have been evaluated or recalculated (cf. Le Fèvre, *loc. cit.*) to allow for this effect. The figures so produced are set out in Table I, which includes, for comparison, certain others (under μ^0) previously given in 1936, together with those (under μ_R) obtained by the refractivity method.

TABLE I.

Apparent moment and polarisation of paraldehyde at 25°.

Solvent or state.	Total pa.	Orientn. pa.	μ^2, D.	μ_E, D.	μ, D.
Gas	87·40	42·9$_5$	—	1·6$_5$	1·44
Light petroleum	109·0$_5$	64·5$_5$	—	1·9$_5$	1·77
Dioxan	119·2$_5$	74·7$_5$	—	2·0$_5$	1·90
Carbon tetrachloride	125·7$_5$	81·2$_5$	2·1$_5$	2·1$_5$	1·98
Benzene	117·0$_5$	73·5$_5$	2·0$_5$	2·0$_5$	1·87
Chloroform	139·4$_5$	94·9$_5$	2·2$_5$	2·2$_5$	2·14
Pure liquid	106·6	62·1	1·8$_5$	1·8$_5$	1·73

Le Fèvre and Russell (*loc. cit.*) also list apparent polarisations in six polar solvents, but the significance of these is doubtful (cf. Glasstone, *Ann. Reports*, 1936, **33**, 134). The questions underlying such measurements, and those of Le Fèvre and Le Fèvre (*J.*, 1936, 487), are now being re-examined on a wider basis in this Department. Where paraldehyde is concerned, therefore, we wish, at this stage, to restrict consideration to the data of the above table, chloroform being retained because it has sometimes been thought admissible as a medium for dipole moment work (cf. Le Fèvre and Rayner, *J.*, 1938, 1921; Caldwell and Le Fèvre, *J.*, 1939, 1614; Calderbank and Le Fèvre, *J.*, 1949, 1462; and the Faraday Soc. List of Dipole Moments, 1934).

Discussion.—The true moment, as determined for the gaseous phase, is surprisingly lower than the apparent moments shown in solution or the liquid state. Paraldehyde is known to undergo spontaneous depolymerisation on heating (Coffin, *Canad. J. Res.*, 1932, **7**, 75; Dacey and Coffin, *J. Chem. Physics*, 1937, **7**, 315), but from the kinetic study of Burnett and Bell (*Trans. Faraday Soc.*, 1938, **34**, 420) it is evident that even at 261° the time of half-change is *ca.* 31 minutes, while below 210° the pressure changes (used as indexes to reaction rates) were scarcely measurable (Coffin, *loc. cit.*). Accordingly, by confining our experiments to temperatures below 200°, and adhering to the timing already specified (Le Fèvre, Ross, and Smythe, *J.*, 1950, 276), we believe we have not incorrectly attributed the observed polarisations to paraldehyde alone, rather than to a changing system, $C_6H_{12}O_3 \rightleftharpoons 3CH_3{\cdot}CHO$.

In terms previously used (Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374; Le Fèvre and Ross, *J.*, 1950, 283) we may summarise the facts thus:

	Light petroleum.	Dioxan.	CCl_4.	C_6H_6.	$CHCl_3$.	Liquid.
$\mu^2_{liq.}/\mu^2_{gas}$	1·51	1·74	1·90	1·69	2·22	1·45
$\Delta\mu/\mu_{gas}$	+0·23	+0·32	+ 0·37	+0·30	+0·49	+0·20

Since the media have been arranged with increasing dielectric constants from left to right, it is obvious that none of the treatments of the " solvent effect " problem in which ε is the controlling factor can be valid for paraldehyde. On the other hand, those theories which involve the shape of the solute, or the algebraic sign of its Kerr constant, appear—qualitatively at least—to be more successful; indeed the $\mu_{liq.}/\mu_{gas}$ ratio now found, although higher than any other yet recorded in the literature, can be roughly forecast by applying Higasi's expressions (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1936, **28**, 284) as though they were intended for polar, as well as non-polar, solvents. Carpenter and Brockway (*loc. cit.*) assign paraldehyde to the first of four models illustrated in their paper. In this, the three oxygen atoms are approximately coplanar with the three methyl-carbon atoms; and these six are 0·47 A. above a parallel plane containing the remaining carbon atoms; C–O and C–C distances of 1·43 and 1·54 A. are also given. All intervalency angles are tetrahedral. A scale drawing of the " elevation " of this skeleton (through one of the oxygens and its opposite CH–Me), after adding outlines corresponding to van der Waals radii, shows that rotation about the direction of action of the resultant moment (cf. Calderbank and Le Fèvre, *loc. cit.*) requires a somewhat flat spheroidal cavity. Several may be drawn but the axial ratios $a : b : c$ are consistently about $\frac{1}{2} : 1 : 1$. Following Higasi, therefore, $k = 2$ in $B = k^3(k^2 - 1)^{-1}\{1 - (k^2 - 1)^{-\frac{1}{2}} \sin^{-1}(k^2 - 1)^{\frac{1}{2}}/k\} - 1/3$, whence $B = 0{\cdot}195$ and $\Delta\mu (= 4\pi n\alpha_{gas}B$, where n and α represent the number of molecules of medium per unit volume and their polarisability respectively) $= 0{\cdot}20 \times 10^{-18}$ e.s.u. Thus the calculated value of $(\mu^2_{liq.}/\mu^2_{gas})$ is 1·30 compared with the 1·45 actually recorded. Further, of course, the fact that ${}_0P_{liq.}/{}_0P_{gas}$ exceeds unity is compatible with θ (in expressions derived from the equation of Raman and Krishnan, *Proc. Roy. Soc.*, 1928, *A*, **117**, 589) having a positive sign, *i.e.*, the reverse of that of the Kerr constant. In view, however, of considerations

prompted by the case of sulphur dioxide (*J.*, 1950, 286), this particular aspect will not be pursued.

According to Onsager (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) the true orientation polarisation of a substance should be $(\varepsilon - n^2)(2\varepsilon + n^2)V/\varepsilon(n^2 + 2)^2$, where V = molecular volume and n is the refractive index for light of infinite wave-length, V and n referring to the condensed phase. Frequently (cf. Böttcher, *Physica*, 1939, **6**, 59; Le Fèvre, Smythe, and Roberts, *J.*, 1949, 902) the use of n_D in place of n_∞ makes only a small difference. Wilson (*Chem. Reviews*, 1939, **25**, 377) recommends that $n_{effective}$, calculated from the distortion polarisation, be adopted instead. With paraldehyde either route gives an extremely high figure: (*a*) n^2_D = 1·989, from $[R_L]_D$ = 33·1, $(_OP)_{calc.}$ = 198 c.c. at 25°; (*b*) $n^2_{eff.}$ = 2·499, from $(_AP + {}_EP)$ = 44·47, $(_OP)_{calc.}$ = 151 c.c. at 25°; $_OP$, calc. *via* $_TP = 44{\cdot}47 + 12792/T$ (cf. p. 290) = 43 c.c. at 25°. Looking over Böttcher's examples, it seems that molecules of the type possessing negative Kerr constants are least satisfactorily handled by the unmodified Onsager formula. (Paraldehyde provides the worst instance to date in our experience.) Onsager, however, was well aware of the limitations imposed by his choice of simplifying and preliminary assumptions (cf. Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43** 391—392). Modifications, giving recognition to the optical anisotropy of the solute, in the manner indicated by Wilson (*loc. cit.*), would certainly improve the situation, but unfortunately neither electric double refraction nor light-scattering studies for gaseous paraldehyde have been made.

With regard to Kirkwood's extension of Onsager's equation (*J. Chem. Physics*, 1939, **7**, 911; *Ann. N.Y. Acad. Sci.*, 1940, **40**, 315), *viz.*, $M(\varepsilon - 1)(2\varepsilon + 1)/9\varepsilon d = {}_EP + {}_AP + 4\pi N\mu^2 g/9kT$, we note (since M/d = 133·5 c.c. and ε_{25} = 12·934; Le Fèvre and Russell, *loc. cit.*) that g is approximately 7·5. This is large (cf. preceding paper for other examples) and would appear to indicate a small value of $(\cos\gamma)_{average}$ in $g = 1 + Z(\cos\gamma)_{Av.}$ where Z is the number of molecules in the first layer around the one under consideration. If Z were about six, and all seven molecular resultant dipoles moving about axes not far from parallel, a model is seen in which maximum "contact" of molecular "areas" is tending to occur. It is relevant to mention, however, that cryoscopically (see following paper) there is no evidence that paraldehyde is "associated" in the ordinary sense of the word.

Finally, the theories based on hindered rotation (*e.g.*, those of Debye, or Kincaid and Eyring, see preceding paper) cannot be applied to paraldehyde, for which $_OP_{liq.}/_OP_{gas}$ is 1·45, since—as was pointed out *a propos* sulphur dioxide—a ratio greater than unity is made impossible by the mathematical forms by which their authors expressed them.

The above paragraphs are chiefly concerned with the *liquid*–gas relationship. We are indebted to Mr. I. G. Ross for some remarks on paraldehyde as a *solute*: using as axes for the spheroid those quoted before (namely 0·5 : 1·0 : 1·0) the Ross–Sack equation is

$$\mu_{soln.}/\mu_{gas} = 3\varepsilon[1 + (n^2_{eff.} - 1)\xi]/(\varepsilon + 2)[\varepsilon + (n^2_{eff.} - \varepsilon)\xi] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where in this case $\xi = (1/e^2) - [(1 - e^2)^{\frac{1}{2}}/e^3]\sin^{-1}e = 0{\cdot}527$, and $e = [1 - (a/b)^2]^{\frac{1}{2}}$. For comparison, the Higasi equation for solutions may be written as

$$\mu_{soln.}/\mu_{gas} = 1 + 3(\xi - 1/3)(\varepsilon - 1)/(\varepsilon + 2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

although it is suggested that the derivation of (2) contains errors and that, with Higasi's approach, the correct form should be

$$\mu_{soln.}/\mu_{gas} = 1 + (\xi - 1/3)\varepsilon/(\varepsilon + 2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The apparent moments in solution, calculated by (1), (2), and (3), are compared below with those actually recorded:

Solvent.	μ, observed.	μ, calc. by (1).	μ, calc. by (2).	μ, calc. by (3).
Vacuum	1·4$_5$	—	—	—
Light petroleum	1·7$_7$	1·7$_1$	1·6$_3$	1·5$_9$
Dioxan	1·9$_5$	1·7$_1$	1·6$_3$	1·5$_9$
Carbon tetrachloride	1·9$_6$	1·7$_2$	1·6$_4$	1·5$_9$
Benzene	1·8$_7$	1·7$_2$	1·6$_4$	1·5$_9$

Equation (1) thus gives slightly better results than does that of Higasi, either in its original (2) or its amended (3) form.

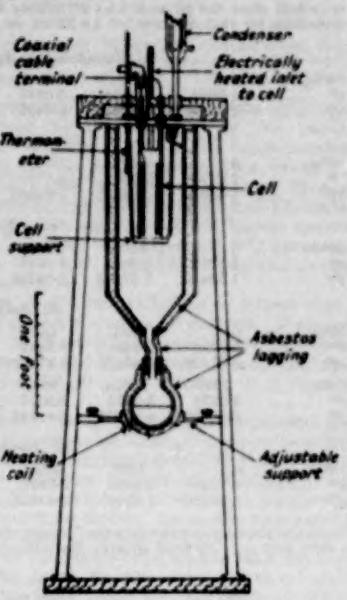
Conclusions.—Paraldehyde is established as a case where the apparent moment, as ordinarily measured in solution *via* the Debye–Clausius–Mosotti route, is markedly greater than the true moment obtained from the gas. The facts now revealed, while out of harmony

with many of the extant theoretical treatments of the problem, are less so with those in which the anisotropy of molecular shape (or polarisability) is significant.

Experimental.

Materials.—The paraldehyde was purified by drying it with anhydrous sodium sulphate and then cooling it to 5°, whereafter the frozen material was separated by decantation. This was distilled (the fraction, b. p. 121—124°, being collected), stored over anhydrous sodium sulphate for several days, and redistilled at atmospheric pressure before use as required.

Polarisation of Gaseous Paraldehyde.—The method of measurement has been essentially that described previously (*J.*, 1950, 276, apparatus B.M.S.) but with the following improvements. The gas cell was replaced by another of similar construction of 124 instead of 80 $\mu\mu$F. capacity (with air). Its leads were brought through the glass walls and soldered directly to the co-axial cable running to the oscillator. For the oil-thermostat, which had been a source of unsteadiness at higher temperatures (due to surface ripples made by the stirrer as the fluid became hotter and more mobile), an all-metal vapour bath, standing on the floor, was substituted. Its details are given in the figure. It had advantages over the glass apparatus of Groves (*J.*, 1939, 1147) in that it was more robust and formed a complete shield, which could be earthed, around the cell. The whole structure was heavily lagged to minimise heat radiation to the electrical components. By the use of chloroform, carbon tetrachloride, xylene, *n*-butyl alcohol, *cyclo*hexanol, benzyl alcohol, and thymol separately at atmospheric pressure, the temperature of the cell could easily be set to within 0·2° or better. The condensates ran back along a guide to flow down the inside wall of the vessel. The rate of boiling was controlled by adjusting the voltage across the heating coil by means of a "Variac" variable transformer.



The new cell was first calibrated against carbon dioxide (see p. 281). Table II shows the values obtained for $\delta C/p$, while the polarisations of paraldehyde follow in Table III.

Table II.

$\delta C/p$ for carbon dioxide.

$T°$, K.	$10^4/T$.	$\delta C/p$.	$(\delta C/p)_{calc.}$	Press. range in cm.	Number of observations.
296·5	3372	7·66	7·662	34—68	10
333·5	2999	6·80	6·800	32—68	13
383·0	2611	5·91	5·905	38—67	13
404·0	2475	5·59	5·592	42—69	11
422·3	2367	5·34	5·342	35—67	12

Whence $x' = (2307{\cdot}0/T) - 0{\cdot}1185$.

Table III.

Paraldehyde.

$T°$, K.	$10^4/T$.	$(\delta C/p)_{p\to 0}$.	P (c.c.).	P (calc.).	Press. range in (cm.).	No. of observations.
386	2591	39·0	77·59	77·61	34—53	13
406	2463	38·2	75·71	75·98	29—61	12
437	2288	32·9	74·09	73·74	25—67	12
457	2188	31·0	71·24	72·46	16—53	11
390 *	2564	61·15	77·4	77·27	25—51	7
473 *	2114	46·60	71·54	71·51	23—36	6

Whence $P = 44{\cdot}47 + 12782/T$ and $\mu = 1{\cdot}44$ D.

Polarisation of Dissolved Paraldehyde.—Apparatus, techniques, and symbols used have been described before (*J.*, 1948, 1949). The solvents were fractionated (after partial freezing where applicable) and

kept over sodium (except carbon tetrachloride, for which calcium chloride was used). The dielectric constants of light petroleum and of dioxan were determined relatively to benzene (2·2725).

The dielectric constants (ϵ^{25}), densities (d_4^{25}), and concentrations (w_1 = weight fraction) are alone recorded, since the polarisations at infinite dilution do not require the separate evaluation of these quantities for each solution (cf. Le Fèvre, *loc. cit.*):

(a) *Paraldehyde in light petroleum* (b. *p.* 94—99°).

10^4w_1	0	9701	19036	28479	57468	79183	
ϵ^{25}	1·9944	2·0158	2·0383	2·0872	2·1376	2·1969	
d_4^{25}	0·74062	0·74212	0·74367	0·74694	0·75023	0·75399	

(b) *Paraldehyde in dioxan.*

10^4w_1	0	11221	15414	23323	40390	46453	54439
ϵ^{25}	2·2172	2·2607	2·2770	2·3086	2·3790	2·4017	2·4347
d_4^{25}	1·02917	1·02883	1·02863	1·02829	1·02762	1·02744	1·02703

(c) *Paraldehyde in carbon tetrachloride.*

10^4w_1	0	11545	19250	49033	72066	108066	
ϵ^{25}	2·2270	2·2986	2·3457	2·5331	2·6733	2·8920	
d_4^{25}	1·58440	1·57338	1·56628	1·53745	1·51644	1·48515	

(d) *Paraldehyde in benzene.*

10^4w_1	0	493	1029	3424	3482	4522	4765	6467
ϵ^{25}	2·2725	2·2851	2·3044	2·3818	2·3832	2·4159	2·4243	2·4802
d_4^{25}	0·87378	0·87410	0·87440	0·87697	0·87750	0·87804	0·87840	0·87996
10^4w_1	7392	8863	9989	10777	12968	16481	20697	
ϵ^{25}	2·3079	2·3674	2·4027	2·4358	2·7159	2·8586	3·0392	
d_4^{25}	0·88082	0·88223	0·88342	0·88412	0·88803	0·88962	0·89417	

(e) *Paraldehyde in chloroform.*

10^4w_1	0	1098	3028	5389	8870	15528
ϵ^{25}	4·7240	4·8459	5·0617	5·3293	5·7204	6·4533
d_4^{25}	1·46814	1·46080	1·44803	1·43258	1·41078	1·38987

From the above measurements the "constants," $\alpha\epsilon_2$ and βd_2 [*i.e.*, $(\epsilon_{12} - \epsilon_2)/w_1$ and $(d_{12} - d_2)/w_1$] show a drift with w_1. By least squares, the following relationships have been fitted:

Solvent.	No. of solns. and w_1-% range.	$\alpha\epsilon_2$	βd_2
Light petroleum	5 (1—8%)	$2·204 + 4·76w_1$	$0·1552 + 0·004w_1$
Dioxan	6 (1—5·4%)	$3·850 + 2·83w_1$	$0·0316 + 0·147w_1$
Benzene	14 (0·5—21%)	$3·067 + 2·78w_1$	$0·0818 + 0·117w_1$
Carbon tetrachloride	5 (1—11%)	$6·207 - 0·30w_1$	$0·293w_1 - 0·9582$
Chloroform	5 (1—15%)	$11·19 \pm 0·0w_1$	$0·294w_1 - 0·6720$

Using the above data at $w_1 = 0$, the polarisations at infinite dilution listed in Table I are calculated as ${}_\infty P_2 = M_1[p_2(1 - \beta) + C\alpha\epsilon_2]$, the requisite values of C and p_2 being:

	Light petroleum.	Dioxan.	Carbon tetrachloride.	Benzene.	Chloroform.
C	0·25388	0·16390	0·10597	0·18809	0·37724
p_2	0·33614	0·28045	0·18321	0·34086	0·04520

Note on the Atomic Polarisation of Paraldehyde.—Since the difference between the distortion polarisation (44·5 c.c.) and the molecular refraction (about 33 c.c.) is *ca.* 11 c.c., paraldehyde must be added to the growing list of cases which disprove the earlier idea that ${}_AP$ might be taken as approximately 10% of ${}_DP$. Coop and Sutton (*J.*, 1938, 1280) and Watson, Kane, and Ramaswamy (*Proc. Roy. Soc.*, 1936, *A*, **156**, 130) have provided the most striking instances. The relative position of the present observations can be seen from the following series of ${}_AP/{}_DP$ ratios:

p-Benzoquinone	0·29	(Coop and Sutton, *loc. cit.*)
p-Dinitrobenzene	0·21	" " "
Beryllium acetylacetonate	0·42	" " "
Ferric "	0·60	" " "
Boron trifluoride	0·46	(Watson, Kane, and Ramaswamy, *loc. cit.*)
Carbon tetrafluoride	0·39	" " "
Silicon tetrafluoride	0·65	" " "
Cyanogen	0·70	" " "
Paraldehyde	0·33	(Present work.)

Comparison with data for a number of ethers is interesting:

	Me_2O.	Et_2O.	Dioxan.	Trioxan.	Paraldehyde.
$_AP$	2·2	4·0	3·0	ca. 13 *	11·4
$_RP$	12·9	21·9	21·6	19·3	33·1

* Calculated from the dielectric constant of solid trioxan at 20° (Walker and Carlisle, *Chem. Eng. News*, 1943, **21**, 1250), *viz.*, $\epsilon = 3{\cdot}2 - 3{\cdot}4$ at 1·6 megacycles. The value of ϵ^{∞} is not given ($\epsilon_D^{20} = 1{\cdot}17$), but has been taken as 1·2 since a higher figure would not appreciably affect $M(\epsilon - 1)/(\epsilon + 2)d = 32$ c.c.

That the three cyclic molecules have similar configurations follows from (*a*) the structural details for paraldehyde recorded by authors cited at the beginning of this paper, (*b*) investigations of crystal structure (Moermann, *Rec. Trav. chim.*, 1937, **56**, 161), dipole moment (Maryatt and Acree, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 71; Calderbank and Le Fèvre, *J.*, 1949, 199), infra-red (Ramsay, *Trans. Faraday Soc.*, 1948, **44**, 289) and Raman spectra (Kohlrausch, *Z. physikal. Chem.*, 1937, *B*, **35**, 29) on trioxan, and (*c*) studies of electron diffraction (Brockway and Sutton, *J. Amer. Chem. Soc.*, 1935, **57**, 473) and infra-red and Raman spectra (Ramsay, *Proc. Roy. Soc.*, 1947, **190**, 563) on dioxan. Oxygen bond angles and C–O distances, where given, are of the same order throughout (*viz.*, 110° ± 5°, and 1·43—1·46 A.) and closely resemble those for dimethyl ether (Brockway and Sutton, *loc. cit.*).

From Sutton's theory of atom polarisation (see p. 283 for references) it follows that: (1) since this quantity depends on polar groups in a molecule whereas $_RP$ does not, $_AP$ cannot be expected to be always the same fraction of $_RP$; (2) if several compounds have essentially common oscillating systems, they have nearly the same $_AP$; and (3) in general $_AP$ is not additive, but in some circumstances (if μ and V_O, in $_AP = 4\pi N\mu^2_1/9V_O$, are constant) it is roughly proportional to the number of polar bonds, or components.

The figures just quoted illustrate these propositions. The $_AP/_RP$ fraction for paraldehyde is not that for many other molecules, although the absolute value of its $_AP$ seems to be of the order of that of trioxan. The angular force constants, V_O, for bending of C–O–C in dimethyl ether and in dioxan are 0·34—0·46 and 0·66 × 10^{12} dynes/cm. respectively (Kohlrausch, *loc. cit.*; Bonner, *J. Chem. Physics*, 1937, **5**, 293); since $_AP = 4\pi Nn\mu^2_1/9V_O$ (where n = the number of oscillating components, *i.e.*, 1 for dimethyl ether and 2 for dioxan), the atomic polarisations for these two molecules should be approximately the same, as in fact they are.

The deformation constants of the C–O–C angles in paraldehyde and trioxan have not been determined. However, Ramsay (*Trans. Faraday Soc.*, 1948, **44**, 289) attempted to calculate the vibration frequencies of the trioxan ring using the same values for the force constants as for dioxan, but differences between his estimates and those observed are large, and indicate that the force constants in trioxan are appreciably smaller than those in dioxan. Nevertheless, if the bending force constant of C–O–C in trioxan (which as a first approximation should be of the same order as that for paraldehyde, as are the C–O bond distances and the C–O–C angles) is closer to that of dimethyl ether, then we would expect an atomic polarisation approaching three times that of dimethyl ether, or 9 c.c. This is in effect the situation found. These results shown the degree of additivity of $_AP$ in these compounds. It resembles that which has also been noticed with certain polyhalides and the metal acetylacetonates (Finn and Sutton, *J.*, 1938, 1250; Coop and Sutton, *loc. cit.*).

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62. *The Apparent Polarisations of Paraldehyde in Non-polar Solvents Measured at* 10 *and* 25 *cm.*

By R. J. W. LE FÈVRE and (MISS) J. W. MULLEY.

Direct observation has verified that, where the common non-polar solvents of low (centipoise order) viscosity are concerned, the results of the preceding paper are not due to a spectrum of relaxation times reaching into the 300-m. region. Signs of dispersion of orientation polarisation may be seen between 25 and 10 cm., but this is credibly reconcilable with the simple Debye formula and accepted molecular dimensions. Solutions of paraldehyde in medicinal paraffin (viscosity *ca.* 0·2 poise) have also been investigated.

THE measurements recorded in this communication were made for precautionary reasons. The time, τ (seconds) of molecular relaxation in a dielectric is given by the well-known equation

of Debye as $\tau = 4\pi\eta r^3/kT$, where η is the macro-viscosity (poises), r is the molecular radius (cm.), k is Boltzmann's constant ($1{\cdot}37 \times 10^{-16}$ ergs/degree), and T is the absolute temperature. If f represents the frequency (in c./s.) of the applied alternating field which corresponds to τ (through the relation $\tau = 1/2\pi f$) we have: $fr^3 = kT/8\pi^2\eta$. Now, the viscosities of the solvents used in the previous work range from 0·2 to 2·0 centipoises. At 25°, therefore, the product fr^3 should be between $2{\cdot}5 \times 10^{-13}$ and $2{\cdot}5 \times 10^{-14}$. Fig. 1 illustrates the consequent dependence of f upon r.

Assuming paraldehyde to be a liquid composed of close-packed spheres, r may be calculated as $0{\cdot}665V^{1/3} \times 10^{-8}$ cm. (V = molecular volume), *i.e.* (since $d_4^{25} = 0{\cdot}990$), 3·40 A. Its viscosity at 20° is 1·18 centipoises (Muchin, *Z. Elektrochem.*, 1913, **19**, 820). Accordingly, if this solute exists in the pure state or in dilute solution (of the type customarily used for dipole moment measurements), as single molecules, its orientation polarisation (${}_OP$) should remain constant until the applied frequency approaches 10^9 c.p.s., *i.e.*, a figure safely distant from that (10^8 c.p.s.) utilised in the preceding paper.

Fig. 1.

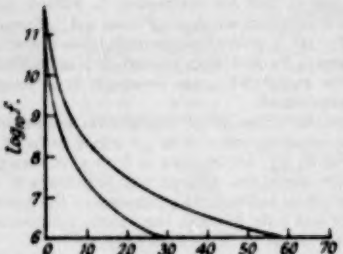
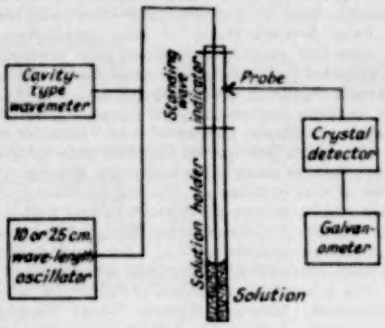


Fig. 2.



However, note should be taken of the following facts: the simple expression of Debye, implying spherical molecules freely rotating against one another and a single relaxation time, is too idealised. It indicates only the *order* of results obtained by direct experiment (cf. Holzmuller, *Physikal. Z.*, 1937, **38**, 574). Most molecules, in fact, would be more accurately regarded as ellipsoids with three axes, for which three values of τ should be foreseen *a priori* (Perrin, *J. Phys. Radium*, 1934, **5**, 497). In at least one instance (Girard and Abadie, *Faraday Soc. Discussion*, 1946, **42**, *A*, 40) dilution has revealed a plurality of dispersion regions. The coefficient of viscosity of flow is only a rough measure of the coefficient of internal friction really required by the Debye relation; for equal concentrations of the same solute in different solvents, maximum dielectric absorption does *not* occur at identical viscosities (Hall, Halliday, Johnson, and Walker, *ibid.*, p. 136). There are indications that the variations are connected with the shapes of the solvent molecules (Thompson, *ibid.*, p. 160). With benzophenone in benzene the incremental loss tangent is still diminishing as f descends past 10^8 c.p.s. (Jackson and Powles, *ibid.*, p. 106); with medicinal paraffin as solvent ($\eta = 1{\cdot}97$ poises) the corresponding point appears to be 10^8 c.p.s.—suggesting the presence of a spectrum of relaxation times.

Now, although cryoscopic studies (Paterno and Nasini, *Ber.*, 1886, **19**, 2529; Luginin and Dupont, *Bull. Soc. Chim.*, 1911, [iv], **9**, 223) in a few solvents have shown paraldehyde to be monomeric, there is still the possibility that in its dielectric behaviour it may act effectively either as double, treble, etc., units (through association, of the cybotactic type with itself) or as a lose structure carrying an " atmosphere " of solvent molecules. Were such to be the case a lower f should follow the greater r. In addition to other uncertainties already mentioned we cannot be sure that the variations of ${}_OP$ just reported have been of the kind we set out to study.

To delimit the possible existence of a similar " spectrum " with paraldehyde we have explored the effects of changing (*a*) the viscosity of the solvent or (*b*) the wave-length of measurement. In the following table we compare our results with those of the preceding paper:

Solvent.	Viscosity, poise.	Wave-length.	$({}_{\infty}P_2)_{25}$, c.c.
Light petroleum	*ca.* 0·003	*ca.* 300 m.	109
Medicinal paraffin	*ca.* 0·2	,,	124—125
Benzene	*ca.* 0·006	,,	117
,,	,,	25 cm.	113—124
,,	,,	10 cm.	102—107

The first two lines show that despite a 60—70-fold increase of viscosity, the total polarisation of paraldehyde is not diminished. It is similarly apparently unaffected by a change of measuring frequency from 10^8 c.p.s. (300 m.) to $1{\cdot}2 \times 10^9$ c.p.s. (25 cm.). The reduction recorded at $0{\cdot}3 \times 10^{10}$ c.p.s. (10 cm.) *may*, however, be real since (i) it appeared also at finite concentrations whenever the same solution was successively examined at the two shortest wavelengths, and (ii) it leads to reasonable estimates for the relaxation time: if ${}_{T}P_{obs.} = 4\pi N[\alpha + \mu^2/3kT(1 + j\omega\tau)]/3$, then $j\omega\tau = ({}_{T}P_{L} - {}_{T}P_{obs.})/({}_{T}P_{obs.} - {}_{D}P)$, where ${}_{T}P_{obs.}$ and ${}_{T}P_{L}$ are respectively the total polarisations observed at angular frequencies, ω, such that for the former $\omega\tau$ is not negligible, ${}_{D}P$ is the distortion polarisation (44·5 c.c. for paraldehyde, cf. preceding paper), and τ is the relaxation time (defined as $\omega\tau = 1$). From our data at 300 m. and 10 cm. (above), $j\omega\tau$ lies between 0·16 and 0·26, whence $T_{25} = 8$—14×10^{-12} secs. That τ is of such an order seems possible from comparison with recorded values for other molecules, *e.g.*, camphor $6{\cdot}2 \times 10^{-12}$ secs. (in *cyclo*hexane at 30°; Whiffen, *J. Amer. Chem. Soc.*, 1948, **70**, 2452), chloroform $7{\cdot}7 \times 10^{-12}$ secs. (in benzene at 19° ± 1°; Jackson and Powles, *Trans. Faraday Soc.*, 1946, **42**, *A*, 101), or acetone $3{\cdot}2 \times 10^{-12}$ secs. (in benzene at 19° ± 2°; Whiffen and Thompson, *ibid.*, p. 118).

We conclude, therefore, that the variations of polarisation registered at 300 m. (preceding paper) are due to solvent influences and not to dispersion effects.

Experimental.

Measurements in Medicinal Paraffin.—The solvent was a commercial sample which had been stored over clean sodium wire for 2 days. It was used without further purification. Procedures followed our standard practice (cf. *J.*, 1948, 1949, and preceding papers, wherein the symbols used below are defined). Results are shown in the following table:

10^4w_1.	ϵ^{25}.	d_4^{25}.	P_1 (c.c.).	10^4w_1.	ϵ^{25}.	d^{25}.	P_1 (c.c.).
0	2·1467 *	0·8510	—	3964	2·2720	0·8543	121·3
2297	2·2193	0·8530	123·0	4435	2·2870	0·8549	121·5

* By direct comparison with benzene, $\epsilon^{25} = 2{\cdot}2725$.

From these, the maximum and minimum values for $\alpha\epsilon_1$ are 3·18 and 3·16, and for βd_1 0·0884 and 0·0845, whence ${}_{\infty}P_1 = 124$—125 c.c.

Measurements at 25 and 10 cm.—These have been made on co-axial equipment, the generators being a cavity tuned lighthouse triode oscillator and a reflex klystron respectively. A general outline of the apparatus is given in Fig. 2. Standard 5/8″ internal diameter, 51 ohm impedance transmission line was used for both the solution holder and the standing wave indicator (the latter was a U.S. War Dept. Type TS-56A/AP model).

The waves are propagated down the line, reflected up through the liquid from the short-circuited end, and the positions of voltage minima of the standing waves, with various depths of liquid in the line, are determined. By plotting the depth of liquid in the line against the distance of the minimum from the surface of the liquid, the wave-length in the liquid can be found. The apparent dielectric constant then follows as $(\lambda_{air}/\lambda_{soln.})^2$.

Since, in general, solutions were made up on different occasions and examined relatively to air—and not the pure solvent, as in ordinary dipole moment work—a separate determination of $\epsilon_{soln.}$ was also made in each case. Hence in the following table, the magnitudes of C $[= 3/d_0(\epsilon_0 + 2)^2]$ and β_0 $[= (\epsilon_0 - 1)/d_0(\epsilon_0 + 2)]$ are not shown as the same for all solutions:

Paraldehyde in benzene.

	Wave-length = 10 cm.			Wave-length = 25 cm.		
10^4w_1	1029	3482	4765	1029	3482	4765
Temp.	23·0°	21·5°	21·3°	22·4°	22·0°	22·0°
d_1	0·8771	0·8813	0·8824	0·8774	0·8809	0·8815
$(\beta_0)^2$	0·3306	0·3389	0·3470	0·3305	0·3391	0·3378
C^2	0·1783	0·1875	0·1837	0·1918	0·1876	0·1882
$(\alpha\epsilon_1)^2$	2·82	2·59	2·77	3·01	3·45	3·27
β^2	0·133	0·124	0·122	0·134	0·128	0·108
${}_{\infty}(_{T}P)^2$	104	103	108	114	125	121
${}_{\infty}(_{T}P)^{25}$	104	120	107	113	124	120

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63. *The Structure of Molecular Compounds. Part VII. Compounds formed by the Inert Gases.*

By H. M. Powell.

Preparation and some properties of the clathrate compound of argon and quinol are described. By crystallisation from water under 40 atmospheres' pressure of argon large and stable crystals containing nearly 9% by weight of argon are obtained. On heating they are converted into α-quinol with liberation of the argon. The volume of argon measured at room temperature and pressure is more than seventy times that of the crystals. Solution of the crystals liberates the gas. Other possible inert-gas compounds are discussed.

In the general series of molecular compounds of formula $3C_6H_4(OH)_2.M$, the component M may be argon. The first preparation of the *compound* was made by slow cooling of a solution of the components in benzene under 20 atm. pressure of argon (Powell and Guter, *Nature*, **1949**, **164**, 240). The solvent was chosen as a result of previous experience in preparing the compound of quinol with carbon dioxide (Part IV, *J.*, **1948**, 61), but the use of benzene results in a comparatively small yield owing to the low solubility of quinol in this solvent. The compound, being of the clathrate type, must be made from a solution containing dissolved molecules of the gas in sufficient concentration to cause the quinol molecules to separate out on cooling in the hydrogen-bonded cage form described as the β-quinol type of structure (Palin and Powell, Part VI, *J.*, 1948, 815). This form, different from the ordinary α-quinol, is produced in the presence of an appropriate concentration of a second component whose molecules are of suitable size to stabilise the cage structure in which they are enclosed.

The present communication deals with new preparations and some properties of the products. The objects of these preparations were to obtain larger quantities of the material, to improve its purity, and to grow large single crystals for other investigations.

In order to obtain a greater concentration of quinol than is possible in a benzene solution, ethanol or water was used as solvent. Methanol was avoided since its molecules, in contrast with those of ethanol, are small enough to be enclosed to form the compound discussed in Part V (Palin and Powell, *J.*, 1948, 571). Water, which is used as solvent in the preparation of the quinol–sulphur dioxide compound, does not give a compound with quinol, but it was at first avoided since it had proved to be unsuitable in an attempted preparation of the carbon dioxide compound at a pressure of 50 atm. However, on trial with argon at somewhat lower pressure it has so far proved to be the best solvent.

The general method of preparation consists in making a solution of quinol saturated at room temperature, placing about 30 c.c. of this in a stainless-steel pressure vessel together with a further portion of quinol approximately equal in weight to the desired yield of compound, washing out atmospheric gases, and applying a pressure of argon from a cylinder, raising the temperature by heating the vessel in a large water-bath, and then allowing the solution to crystallise by slow cooling. The argon pressure is maintained by suitable additions from the cylinder.

The quantity of quinol taken should be such that it will dissolve when the temperature is raised. Usually much less was used than would have dissolved, and even so, considerable amounts of α-quinol sometimes came out with the compound. This is presumably due to a too rapid deposition of material with local impoverishment of the solution with respect to argon. The formation of the crystalline product takes place in the last stages of the cooling.

The need for a high pressure of argon is due to the low solubility of the gas. In the absence of any strong interaction between argon and quinol, the clathrate compound is formed by arranging for an argon atom to be available in position at the surface of the growing crystal whenever a cage of quinol molecules links up through its hydrogen bonds. The pressure is not required to prevent dissociation, since once the argon atom is enclosed it is retained by the strength of its cages, so that if sufficient time were allowed for the growth of the crystal it might form from a solution of very low argon concentration. For ordinary rates of crystallisation, obtained by allowing the water-bath to cool in the air, the pressure required to prevent local impoverishment of the solution might be expected to be of the same order of magnitude as that which the argon contained in the crystalline product would have if its cage surroundings were removed. From the known dimensions of the cages, which vary slightly but in a predictable way according to the dimensions of the enclosed molecule (Part VI), the volume of crystalline substance of formula $3C_6H_4(OH)_2.A$ which contains one g.-atom of argon is calculated to be approximately 260 c.c. This quantity of argon in the form of a gas

Photomicrograph of part of a mixed product. The large rhombohedra are crystals of the argon-quinol compound. The needles are α-quinol. Magnification × **40.**

[*To face p.* 399.

occupying the same volume at 15° has a calculated pressure of 91 atmospheres. The present series of preparations has been made with argon at pressures up to 40 atmospheres. As is commonly the case with compounds of this type (Part VI), the quantity of argon is below that corresponding to the ideal formula owing to some cavities being left empty. The product of highest argon content so far obtained has the composition $3C_6H_4(OH)_2{\cdot}0{\cdot}8A$, and therefore contains argon equivalent to a pressure of 73 atmospheres.

Observations on some prepared samples are given below. Argon contents were determined either from the weight of quinol recovered after liberation of argon by dissolution of the material in ether, or by heating the substance to 130°. For heating, the material is contained in a closed vessel to avoid loss of quinol which slowly sublimes. After the vessel has cooled, the liberated argon is displaced by air, and the weight of quinol residue determined. The nature of the crystalline samples was also examined in other ways. Crystals of the quinol–argon compound liberate large volumes of gas when covered with methanol which dissolves quinol, and, although α-quinol crystals sometimes give off a small amount of gas, there is no difficulty in distinguishing the two. With the aid of the microscope, or without it in the case of large crystals, the argon–quinol crystals may be recognised by their stumpy hexagonal prism form with terminal rhombohedral faces, or by their occurrence as rhombohedra of the type illustrated in the photomicrograph. Crystals of α-quinol were always very thin hexagonal needles, often striated lengthwise, and their terminal faces were usually indistinct. Differences in refractive indices could be used to distinguish the two materials but were not much employed since they are affected by the variation in composition of the compound. Single-crystal *X*-ray photographs give a sure proof of the presence of a component, and powder photographs were also employed for identification since a more representative sample of a mixed product is obtained by powdering a larger quantity. A preliminary trial showed that the compound is not affected by powdering. Differences of density make it possible to separate the constituents by flotation, but this procedure is not very effective since the densities vary on account of variable composition, occlusions in the crystals, and the tendency of the crystals to form aggregates.

Experimental.

(1) From 60 c.c. of benzene solution at 34 atm., 0·4 g. of product [Found: A, 4. Calc. for $3C_6H_4(OH)_2{\cdot}A$: A, 10·8%] was obtained. The product contained needle-shaped α-quinol together with larger crystals of the argon compound in the form of rhombohedra. The difference is shown in the photomicrograph. As far as possible a mechanical separation was made. Both types of crystal are colourless and some of the argon-containing crystals are more needle-like than those shown in the photograph. This makes the separation difficult and the analysed portion is of uncertain purity.

(2) From 30 c.c. of ethanol solution at 40 atm., 5 g. of product (Found: A, 3·5%) were obtained. The crystals were of needle habit but usually of a more stumpy appearance than those of α-quinol, from which they may also be distinguished by their terminal rhombohedron faces when these are visible. The product contained some α-quinol.

A glass apparatus was constructed so that a known weight of the product could be placed in a bulb. A space above the crystals could be evacuated by means of a Hyvac pump and then isolated from the pump by a tap. The space, consisting of bulb and connecting tubes, was bounded by the surface of mercury in an attached manometer, and could be restored to a fixed volume by manipulation of the manometer until this mercury surface reached the fixed mark attained when the system was first evacuated. The volume of this space was determined by observing the temperature and pressure when a known mass of air was admitted from a second bulb, and, after the apparatus had been dismantled, was checked by the weight of water required to fill it, with allowance for the volume of crystals.

When the bulb containing a portion of the compound was heated slowly, the evolution of argon could be followed by observation of the manometer. The pressures observed were not equilibrium pressures and at any time the mercury level could be restored to its original position in order that the pressure might be read for a fixed volume of gas. After the evolution of gas at higher temperature, lowering of the temperature to a former value did not result in a decrease in pressure to the value previously observed at the lower temperature. At 40° gas was given off very slowly, the pressure being 1 mm. (compared with 762 mm. when all argon was liberated). At 70° a pressure of 29 mm. was observed, and this rose in the course of 5 minutes to 39 mm. Forty minutes later, after the temperature had been taken to 100°, the pressure recorded on restoring the temperature to 70° was 391 mm. The liberation of argon is very nearly complete at 130°, and at this temperature the solid has been converted into α-quinol. Raising the temperature until the quinol melts causes no appreciable change in the total amount of gas. The final pressure of the gas, at the fixed volume, was measured at room temperature, and, since the mass of gas liberated from the original weighed quantity of material was known, the density of the gas was calculated. The values observed, 0·0010 g./c.c., were usually slightly higher than the density of argon (0·0018 g./c.c. at N.T.P.). The argon used was spectroscopically pure, and the discrepancy is probably due to the argon content of the specimen being slightly over-estimated. The behaviour has not been fully investigated but it is known that a slight loss of weight occurs slowly when certain samples of the argon compound are kept either in the atmosphere or in a desiccator. It may be due to the removal of small amounts of adhering solvent or to the escape of some argon. In either case this would mean that the true argon content of a sample

from which the argon was released and measured would be less than that derived from an analysis carried out before the material was used, and thus would lead to a high value for the density.

(3) From 30 c.c. of aqueous solution at 40 atm., the argon–quinol compound was obtained in large single crystals in the form of hexagonal prisms with terminal rhombohedron faces. Some of these crystals were nearly 1 cm. long and several mm. in breadth. They were accompanied by crystals of α-quinol which always form as very thin needles. Separation of the two products could therefore be carried out by hand picking or by sieving, and the two parts examined separately. With other conditions kept as far as possible the same, the weight of product was varied by variation of the quantity of quinol used in the preparation. A yield of 6 g. was separated into nearly equal weights of α-quinol and the compound; one 3-g. yield contained at least 2·9 g. of the compound and very little α-quinol. However, the relative amounts of α-quinol and the compound obtained in different preparations in similar conditions were not constant, and it seems probable that the proportions are sensitive to conditions such as the frequency of formation of crystal nuclei which were not accurately controlled. However, the great ease of separation of the two constituents as formed from aqueous solution ensures an uncontaminated yield of the compound. The argon content in a typical sample was 8·8%, corresponding to 60% of the maximum possible argon content. An even greater proportion of occupied cavities may be expected with the more soluble heavier inert gases and the corresponding xenon compound should contain as much as 28% by weight of the inert gas.

Crystals of the argon compound have been preserved for weeks without visible change but some samples have been observed to lose weight, so far less than 1%. Some time will be necessary for the further examination of the keeping properties of the compound. Small quantities of solvent, which by successive attacks on different parts of the structure may detach quinol molecules, may cause the liberation of argon. It seems probable that in suitable conditions the compound would be a convenient portable source of argon, and the compounds of the heavier inert gases could be used similarly. The fact that the stable compound already prepared retains argon effectively at more than 70 atm. pressure is sufficient demonstration of the reality of the imprisoning action which is the basis of the concept of clathrate compounds. A fuller description of the relation of the argon atom to its surroundings is to be given with the crystal structure determination of the compound.

Some preliminary experiments were made concerning other possible compounds of similar type. All were carried out with 40 atm. pressure of inert gas, and in every case a preparation which had resulted in the formation of the argon compound was repeated with the substitution of another substance for quinol or for argon. The crystalline products were dissolved in suitable solvents and in no case was there any evolution of inert gas. Thus no compound was formed between argon and resorcinol, *p*-aminophenol, or *p*-phenylenediamine from ethanol solutions. Substitutes for quinol may be found among other substances capable of hydrogen-bond formation or in other classes of compound, but any exact prediction does not seem possible at present. No compound was formed between quinol and helium from benzene solution. The product was identified as α-quinol. This expected result may be explained by the small effective size of the helium atom, well known for its power of penetrating small spaces. The compound does not form because the helium atom cannot be retained by the quinol cages. A further attempt to prepare the helium–quinol compound in more favourable conditions is projected. It is not known whether neon will give a compound with quinol; it seems certain that the heavier inert gases will do so. Examination of these possibilities is intended.

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64. *The Structure of Molecular Compounds. Part VIII. The Compound of Krypton and Quinol.*

By H. M. POWELL.

By crystallisation of an aqueous solution of quinol under 20 atmospheres pressure of krypton the clathrate compound of composition $3C_6H_4(OH)_2{\cdot}0{\cdot}74Kr$ [ideally $3C_6H_4(OH)_2{\cdot}Kr$] is obtained in a form similar to that of the corresponding argon compound.

THE general series of clathrate compounds of ideal formula $3C_6H_4(OH)_2{\cdot}M$ formed by quinol with a variety of substances M, which in their ordinary states at room temperature may be volatile liquids or gases, owe their existence to the formation by quinol, in the presence of the second component, of a special cage-like structure which imprisons single molecules M each in its own cavity. No ordinary chemical bonds are needed between quinol and the other molecule.

From the general properties and modes of formation it was suggested (Part IV, *J.*, 1948, 61) that the inert gases would form such compounds if a solution of quinol under high pressure of the inert gas were allowed to crystallise. The argon compound has already been prepared (Powell and Guter, *Nature*, 1949, **164**, 240; Powell, Part VII, preceding paper), but the helium compound appears not to exist. As discussed in Part IV, the enclosed molecule must satisfy certain requirements of size and shape. It must not be too large for the space available in the cavity although minor modifications in the shape of the enclosing quinol framework may be

made to accommodate different molecules (Palin and Powell, Part VI, *J.*, 1948, 815). For a small effectively spherical molecule such as hydrogen chloride which does not completely fill the cavity, the two interpenetrating hydrogen-bonded quinol frameworks, which together form the walls of the enclosing cavities, adjust themselves to the equilibrium positions that they would occupy in the absence of any enclosed component, but for non-spherical molecules such as methyl cyanide the quinol structure distends in the manner of a piece of trellis. For enclosure of the inert-gas atoms the undistended form is to be expected and has been found for the argon compound. The absence of a helium compound is attributed to the small effective size of the atom, which could escape through a hole in the cage walls provided by six oxygen atoms linked through hydrogen bonds of length 2·75 A. along the sides of a plane hexagon. As shown in Part VI, a very slight distension of the quinol structure occurs when the methanol molecule is enclosed, and a molecule considerably larger than that of methanol, *e.g.*, methyl cyanide, will fit into the cavity by arranging its length in a way that fits the surrounding structure. The van der Waals radius for a CH_3 group in crystals is about 2 A., and it is therefore expected that spherical atoms of this size and somewhat larger will be enclosed and retained by the cages. From crystal-structure examinations the radii of the inert-gas atoms (for temperatures at which these substances solidify) are Ne 1·61, A 1·9, Kr 2·0, Xe 2·2 A. The radii for room temperature will be somewhat greater. The krypton atom, intermediate in size between argon and the methyl group, should therefore form a compound, and it seems probable that the xenon atom which is not much larger than a methyl group will be capable of enclosure in the same way. The solubilities in water of the inert gases increase with increasing atomic number, and since the higher solubility increases the chance of an inert-gas atom being available in the right place for enclosure, it may be expected that the compound will form more readily the higher the atomic number.

The krypton compound has now been prepared. 60 C.c. of a solution of quinol in water saturated at room temperature were contained in a pressure vessel with a further 2 g. of quinol. A pressure of 20 atm. of krypton was applied from a cylinder of the gas. The temperature was raised to 95° in order to dissolve the additional quinol, and the solution allowed to cool during 12 hours. The product consisted of crystals, some several mm. in thickness, similar in appearance to those of the argon compound, and distinguishable from a small amount of fine needles of α-quinol which also came out. A complete separation could not be made, and an analysed sample probably contained a small proportion of α-quinol. When heated to 120° with precautions to prevent loss of quinol by volatilisation, it lost 14·3% by weight. This corresponds to a composition $3C_6H_4(OH)_2.0{\cdot}67Kr$. As was expected, a somewhat higher krypton content was calculated from the density of a single selected crystal of the compound. This gave by flotation $d = 1{\cdot}51$ g./c.c., and for a unit cell of the same size as the argon compound this corresponds to 15·8% krypton content, *i.e.*, a composition $3C_6H_4(OH)_2.0{\cdot}74Kr$. Thus about three-quarters of the available cavities are occupied by krypton atoms. This may be compared with the 80% occupancy in the argon compound made in similar conditions but under 40 atmospheres' pressure. The procedure of the preparation excludes all possibility of anything but krypton being available for enclosure, and the high density cannot be explained except by the presence of these heavy atoms. Addition of methanol to the crystals causes dissolution with vigorous effervescence owing to liberation of krypton.

The author expresses his thanks to the British Oxygen Co., who provided a cylinder of krypton at the required pressure.

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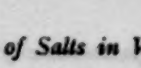
65. *The Extent of Dissociation of Salts in Water. Part XII. Calcium Salts of Some Amino-acids and Dipeptides.*

By C. W. Davies and (Mrs.) G. M. Waind.

The calcium ion has a marked tendency to associate with the anions of α-amino-acids in the following way: $Ca^{\cdot\cdot} + A' = CaA^{\cdot}$. The stabilities of a number of such association products of calcium with amino-acids and dipeptides are reported and discussed.

In a previous paper (*J.*, 1938, 277) it was shown that the aminoacetate anion, like the anions of α-hydroxy-acids, has a strong tendency to associate with the calcium ion in aqueous solution,

and it was suggested that a chelate structure  was possibly responsible for this.

We have now extended this work to a number of other amino-acids and dipeptides at 25°, using the same method as before: the enhanced solubility of calcium iodate in a solution of the sodium salt of the amino-acid gives, after correction for interionic effects, a direct measure of the association of calcium with the added anion.

Experimental.

Materials.—Calcium iodate hexahydrate was prepared, and the solubility measurements were made, in the manner described previously (*J.*, 1938, 273, 277). Where only small amounts of saturating salt were available, as with the dipeptides and di-iodotyrosine, a smaller saturator was used, and the titrations were carried out on 10-ml. samples of the saturated solution.

The purity of the acids and dipeptides was checked by carrying out differential potentiometric titrations of their solutions against standard sodium hydroxide, using an "alki" electrode for pH's greater than 9, and applying the corrections of Jordan and Taylor (*J.*, 1946, 994). Stock solutions of the sodium salts were then made up in accordance with the observed end-points.

Sodium aminoacetate.

m.	s.	K.
0	7·84	—
28·35	9·55	0·037
56·70	10·81	0·037
74·70	11·40	0·039
149·4	13·77	0·036
	Mean	0·037

Sodium α-aminopropionate.

m.	s.	K.
19·62	8·96	0·057
21·08	8·99	0·060
31·63	9·45	0·058
42·17	9·85	0·059
52·72	10·24	0·058
63·27	10·61	0·057
73·80	10·92	0·058
84·35	11·26	0·056
98·64	11·58	0·060
109·6	11·70	0·060
	Mean	0·058

Sodium salt of serine.

m.	s.	K.
11·22	8·62	0·034
21·10	9·20	0·036
56·10	10·68	0·040
	Mean	0·037

Sodium salt of glycylglycine.

m.	s.	K.
11·55	8·51	0·060
13·06	8·56	0·053
23·10	9·04	0·053
34·65	9·55	0·060
48·52	10·05	0·061
	Mean	0·057

Sodium salt of alanylglycine.

m.	s.	K.
61·22	9·83	0·22

Sodium salt of leucylglycine.

m.	s.	K.
52·55	9·61	0·20

Sodium salt of tyrosine.

m.	s.	K.
19·09	9·02	0·028
32·20	9·69	0·038
35·89	9·98	0·034
	Mean	0·033

Sodium salt of di-iodotyrosine.

m.	s.	K.
18·64	9·17	0·028
41·89	10·44	0·029
	Mean	0·029

Sodium hippurate.

m.	s.	K.
24·15	8·76	0·42
25·14	8·81	0·35
48·36	9·45	0·35
50·22	9·48	0·37
	Mean	0·37

Monosodium glutamate.

m.	s.	K.
22·22	8·87	0·071
23·60	9·06	0·060
44·50	9·86	0·065
46·47	9·92	0·067
90·26	11·05	0·068
92·85	11·14	0·068
	Mean	0·067

Disodium glutamate.

m.	s.	K.
5·62	8·68	0·0092
11·42	9·34	0·0096
21·43	10·42	0·0080
22·49	10·44	0·0083
	Mean	0·0088

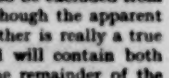
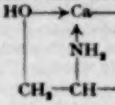
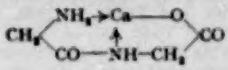
Results.—These are given in the table. Col. 1 shows the concentration of the added salt, and col. 2 the measured solubility of calcium iodate hexahydrate, both in millimols. per litre. Col. 3 gives the calculated dissociation constant, $K = f_{Ca}f_A[Ca][A]/f_{CaA}[CaA]$, [A] being the concentration of the added anion. The calculations were made as in the earlier papers. The saturated solution contains $Ca^{··}$, IO_3', Na^+, A', and their possible association products, $CaIO_3^+$, $NaIO_3$ and CaA^+; NaA was assumed to be completely dissociated. The composition of the solutions was obtained by successive approximations from the known dissociation constants of $CaIO_3^+$, $K = 0·13$, and of $NaIO_3$, $K = 3·0$ and from the solubility product $(Ca^{··})(IO_3')^2 = 7·119 \times 10^{-7}$, using Davies's activity equation (*J.*, 1938, 2093). In the case of the disodium glutamate solutions, which are extensively hydrolysed, allowance had also to be made for the species OH', $CaOH^+$, HG' and $CaHG^+$ (G representing the doubly charged glutamate ion).

Discussion.

Greenwald (*J. Physical Chem.*, 1939, **43**, 379) has studied the association between magnesium and aminoacetate (glycine) ions, and has concluded that the formulation: $Mg^{··} + 2G' \rightleftharpoons MgG_2$ fits the data better than does $Mg^{··} + G' \rightleftharpoons MgG^+$; this is contrary to the assumption we have used here and in the earlier paper quoted above. The data available to Greenwald were not very numerous or concordant, and our long series of solubility measurements with alanine was carried out to test the two possibilities more thoroughly. It will be seen that the K values derived for the $CaAl^+$ ion leave little to be desired as regards constancy, and we conclude that

up to a concentration of 0·1M. the tendency for association to go beyond the first stage is negligibly small. This agrees with what has been found previously for the association between the calcium ion and the anions of α-hydroxy-acids (*J.*, 1939, 279).

Of the eleven series of measurements reported in the Table, those involving the glutamic acid salts must be considered separately. The value $K = 0·0088$ for calcium glutamate comes between the dissociation constants found by Topp and Davies (*J.*, 1940, 87) for calcium succinate (0·010) and calcium adipate (0·0064); there is no evidence that the amino-group exerts any influence in this case. In the monosodium glutamate solutions the anion is believed to be mainly $CO_2^-{\cdot}CH_2{\cdot}CH_2{\cdot}CH(NH_3^+){\cdot}CO_2^-$, and this, in its association with the calcium ion, is not comparable with the other anions studied. In seeking for relationships between dissociation constant and structure, the data for tyrosine and di-iodotyrosine should also be excluded from the comparison. Both these compounds contain phenolic groups, and although the apparent constants reported in the table seem satisfactory, it is probable that neither is really a true constant for a single dissociation process, since the solutions studied will contain both $CO_2^-{\cdot}CH(NH_3^+){\cdot}R{\cdot}OH$ and $CO_2^-{\cdot}CH(NH_3^+){\cdot}R{\cdot}O^-$ (where R represents the remainder of the molecule).

The remaining seven constants all refer to univalent cations which will dissociate into Ca^{++} and ions of formula $NHR{\cdot}CHR_1{\cdot}CO_2^-$. They cover a ten-fold range, from $K = 0·037$ for the glycine salt, which is certainly abnormally weak, to $K = 0·37$ for the hippurate, where the benzoylated amino-group would not be expected to exert any influence, and which is almost completely dissociated in dilute solution. So far as the figures go, they are consistent with the following two hypotheses: (*a*) that the tendency to form a chelate structure  is rapidly reduced by weighting the glycine molecule with extraneous groups R or R_1; and (*b*) that the possibility of a tridentate configuration will enhance the tendency to associate with the calcium ion; this would account for the low constants found for serine and glycylglycine, where the structures  and  would be possible.

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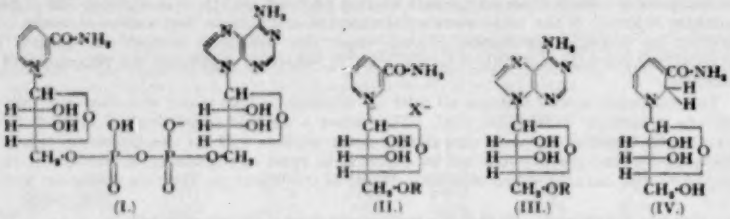
66. *Codehydrogenases. Part I. The Synthesis of Dihydronicotinamide-D-ribofuranoside* [*N*-D-*Ribofuranosidyl*-1 : 2(*or* 6)-*dihydronicotinamide*].

By L. J. HAYNES and A. R. TODD.

As a first step in a projected synthesis of cozymase, a number of *N*-glycosidyl-3-carbamylpyridinium bromides and their reduction products, the dihydronicotinamide glycosides, have been prepared, including a *dihydronicotinamide*-D-*ribofuranoside* [*N*-D-*ribofuranosidyl*-1 : 2(or 6)-*dihydronicotinamide*], probably identical with the dihydronicotinamide nucleoside prepared from natural cozymase. The formation of two (probably α- and β-) isomeric glucosides by condensation of α-acetobromoglucose with nicotinamide has been observed, and it is shown that quaternary glycosides can be formed from nicotinamide with both *cis*- and *trans*-acetobromosugars.

In recent years an extensive series of investigations has been undertaken in this laboratory, aimed at the clarification of structural problems in the nucleotide field by application of synthetic methods. One of these problems is the verification of the structures proposed for the so-called nucleotide coenzymes (adenosine di- and tri-phosphates, coenzymes I and II, and flavin-adenine-dinucleotide). Investigations leading to the synthesis of the natural purine and pyrimidine ribonucleosides and the development of methods of phosphorylation and polyphosphorylation have been described in papers published in this Journal (for summarised accounts see Todd, *J.*, 1946, 647; Lythgoe and Todd, *Symp. Soc. Exp. Biol.*, 1947, **1**, 15; Todd, *Bull. Soc. chim.*, 1948, 933). On the basis of these studies it was possible to effect the total synthesis of the cophosphorylases adenosine diphosphate (Baddiley and Todd, *J.*, 1947, 648) and adenosine triphosphate (Baddiley, Michelson, and Todd, *Nature*, 1948, **161**, 761; *J.*, 1949, 582). In

continuation of our studies we have now devoted attention to the problem of a synthesis of cozymase (coenzyme I, codehydrogenase I, diphosphopyridine nucleotide), which acts as coenzyme in a number of biological oxidations. As a result of researches by von Euler, Schlenk, Warburg, and Karrer (for review see Lythgoe, *Ann. Reports*, 1945, **42**, 175) structure (I) has been advanced for cozymase mainly as a result of degradative work on this substance and the related coenzyme II (codehydrogenase II, triphosphopyridine nucleotide). Although the evidence for structure (I) seems conclusive, a total synthesis would be very desirable, not merely for purposes of confirmation, but also because it might make the substance more accessible in a pure condition and because it might be possible to apply the synthetic method to the production of a variety of structural analogues with which some study of the specificity of the coenzyme might be undertaken, or antagonists to it be discovered.



(I.) (II.) (III.) (IV.)

The problem of a total cozymase synthesis in its most elementary form resolves itself into three parts: (1) the synthesis of "nicotinamide nucleoside" (II; R = H) and adenosine (III; R = H), (2) the phosphorylation of (II) and (III) to the corresponding nucleotides [II; R = $PO(OH)_2$] and [III; R = $PO(OH)_2$], and (3) the linkage of these nucleotides to yield cozymase. Of these various parts, adenosine (III; R = H) (Davoll, Lythgoe, and Todd, *J.*, 1948, 967; Kenner, Taylor, and Todd, *J.*, 1949, 1620) and adenosine-5′ phosphate [III; R = $PO(OH)_2$] (Baddiley and Todd, *loc. cit.*) have already been synthesised. The present communication deals with the synthesis of the dihydronicotinamide riboside (IV). In (IV) the formulation as a 1 : 2-dihydronicotinamide derivative is arbitrary; whether it is a 1 : 2- or 1 : 6-dihydro-compound is at present unknown (cf. Karrer, Schwarzenbach, Benz, and Solmssen, *Helv. Chim. Acta*, 1936, **19**, 811; Karrer, Schwarzenbach, and Utzinger, *ibid.*, 1937, **20**, 720).

The first recorded synthesis of a glycosidylpyridinium salt is due to Fischer and Raske (*Ber.*, 1910, **43**, 1750), who prepared *N*-2′ : 3′ : 4′ : 6′-tetra-acetyl D-glucosidylpyridinium bromide by allowing α-acetobromoglucose to react with pyridine in presence of phenol. In the course of the researches leading to the formulation of cozymase as (I) and the recognition that the active centre of the molecule in biological hydrogen transfer is the quaternary ammonium grouping (reversible reduction to a dihydro-compound), Karrer, Ringier, Büchi, Fritsche, and Solmssen (*Helv. Chim. Acta*, 1937, **20**, 55) extended the work of Fischer and Raske to the preparation of several related compounds. Acetobromoglucose, acetobromoarabinose, and acetobromoxylose were condensed with nicotinamide in dioxan solution and, in the case of acetobromoglucose, condensations were also carried out with other derivatives of nicotinic acid. In these experiments the preparation and purification of the pentose derivatives seem to have been troublesome, since analytical values are recorded only for the nicotinamide arabopyranoside. These quaternary salts showed oxidation–reduction properties similar to those of cozymase. That the nicotinamide–ribose linkage in cozymase was similar to that present in the synthetic materials was later shown by enzymic hydrolysis of the coenzyme with the nucleotidase obtained from sweet almond press-cake. This hydrolysis yielded adenosine and a "nicotinamide nucleoside" which, although devoid of coenzyme activity, showed properties analogous to those of Karrer's model substances. The "nicotinamide nucleoside" was an amorphous hygroscopic powder which retained moisture even when dried in a high vacuum (Schlenk, *Naturwiss.*, 1940, **28**, 46; *Svensk Akad. Kemi*, 1941, **14**, *A*, 13; *J. Biol. Chem.*, 1942, **140**, 619; *Arch. Biochem.*, 1943, **3**, 93; Schlenk and Gingrich, *J. Biol. Chem.*, 1942, **143**, 295; *J. Bact.*, 1944, **47**, 535).

We have further extended Fischer's synthesis to include the preparation of quaternary salts from nicotinamide and acetohalogeno-derivatives of D-mannopyranose, D-galactopyranose, and D-ribofuranose and have repeated the preparation of the D-glucose and L-arabinose derivatives already described by Karrer *et al.* (*loc. cit.*). The successful formation of a quaternary salt from α-acetobromo-D-mannopyranose calls for some comment. It has been stated by Micheel

and Micheel (*Ber.*, 1930, **63**, 390; 1932, **65**, 253) that acetohalogeno-sugars, in which the halogen atom on $C_{(1)}$ is in the *trans*-position with respect to the acetyl groups at $C_{(2)}$ and $C_{(3)}$, will not react with tertiary bases to form quaternary salts, and that reaction with a tertiary amine to form a quaternary salt is diagnostic of a *cis*-acetohalogeno-sugar. α-Acetobromo-D-mannopyranose has, of course, a *trans*-configuration, and since it does form a quaternary salt with nicotinamide it is clear that the rule of Micheel and Micheel is not absolute. The German workers based their conclusions on experiments in which they attempted to cause acetobromomannose, acetochloromannose, and other acetohalogeno-sugars to react with trimethylamine in benzene, ethanol, or a mixture of these two solvents at room temperature or in sealed tubes at 100°. Examination of their results shows that, in experiments where no quaternary salt was formed, either starting materials were recovered unchanged (room-temperature experiments) or gross decomposition occurred (sealed-tube experiments at 100°).

In our early attempts to condense nicotinamide with α-acetobromo-D-mannopyranose (which we selected as a model compound in view of the configurational similarity of mannose and ribose), the two compounds were heated together under reflux for some hours in methyl cyanide solution. Although this procedure had given an excellent yield of quaternary salts with α-acetobromo-D-glucopyranose, no quaternary salt was formed, the main reaction being dehydrohalogenation of the sugar derivatives with formation of nicotinamide hydrobromide. Further experiments showed that, if the solution of the reactants was maintained at 40—50°, comparatively little nicotinamide hydrobromide was formed and *3-carbamyl-N-2′ : 3′ : 4′ : 6′-tetra-acetyl-D-mannopyranosidylpyridinium bromide* was produced in a yield of some 60%. A series of experiments on the general problem of the formation of quaternary salts from nicotinamide and acetohalogeno-sugars showed that acetofluoro-sugars are too unreactive to undergo either quaternary salt formation or dehydrohalogenation, while acetochloro-sugars (including α-acetochloro-D-glucopyranose) react more slowly than the corresponding bromo-compounds and undergo only the dehydrohalogenation reaction. Apparently quaternary salt formation and dehydrohalogenation are simultaneous competing reactions when acetobromo-sugars are used. Higher temperatures favour dehydrohalogenation, and in the case of the *trans*-acetobromo-sugars a difference of 30—40° in temperature may mean that the quaternary salt is formed almost exclusively or not at all. The " rule " of Micheel and Micheel has thus no general significance as a means of determining configuration in an acetohalogeno-sugar. Fischer and Raske (*loc. cit.*) reported that two forms of the quaternary acetylated glucoside were produced by condensation of pyridine with α-acetobromo-D-glucose. These two forms differed markedly in their physical properties, the first ($[\alpha]_D^{20} = -6{\cdot}43°$) being a crystalline compound, insoluble or sparingly soluble in organic solvents, and the second ($[\alpha]_D = +16{\cdot}2°$) an amorphous, very hygroscopic solid, easily soluble in methyl ethyl ketone but insoluble in ether. We have found that the condensation of nicotinamide with α-acetobromo-D-glucopyranose in methyl cyanide solution proceeds similarly; in addition to the crystalline compound ($[\alpha]_D^{20} = -18{\cdot}3°$) isolated by Karrer *et al.* (*loc. cit.*), it is possible to isolate an isomeric substance as a very hygroscopic amorphous solid, easily soluble in methyl cyanide, chloroform, and ethanol, and insoluble in ether ($[\alpha]_D^{20} = +20{\cdot}9°$). These two products are almost certainly α,β-isomers. With other acetobromo-sugars we obtained only amorphous glycosides and in no case were we able to obtain two distinct compounds; the possibility that some of these amorphous products may be mixtures of α- and β-forms cannot be excluded.

Reduction of the quaternary salts prepared from nicotinamide and acetobromo-D-glucopyranose, acetobromo-D-galactopyranose, acetobromo-D-mannopyranose, and acetobromo-L-arabopyranose with sodium dithionite yielded the corresponding acetylated dihydronicotinamide glycosides which could be readily reoxidised. It was found advantageous to carry out these reductions in an inert atmosphere and to avoid undue exposure of the products to light. The acetylated dihydro-glycosides were readily deacetylated with methanolic ammonia. With the exception of the glucose derivative already described by Karrer *et al.* (*loc. cit.*), all the compounds prepared were amorphous and hygroscopic and have so far defied all attempts at crystallisation; in the case of the quaternary salts, variation of the acid radical also failed to yield crystalline products. There can, however, be little doubt of their homogeneity, since repeated fractional precipitations gave products which showed no significant differences in physical or chemical characteristics. Mild acid hydrolysis of the quaternary acetylated galactoside gave *3-carbamyl-N-D-galactopyranosidylpyridinium bromide*, which was also amorphous.

Condensation of acetobromo-D-ribofuranose (Howard, Lythgoe, and Todd, *J.*, 1947, 1052) with nicotinamide gave a quaternary salt reduced by sodium dithionite to *dihydronicotinamide-*

(2′ : 3′ : 5′-*triacetyl* D-*ribofuranoside*) and from this product *dihydronicotinamide*-D-*ribofuranoside* [N-D-*ribofuranosido*-1 : 2(or 6)-*dihydronicotinamide*] (IV) was prepared as a pale yellow amorphous hygroscopic powder by deacetylation. It is not yet possible to say with certainty that this synthetic product is identical with Schlenk's dihydronicotinamide nucleoside, since the latter has been rather inadequately characterised, and in the absence of direct comparison the possibility that the natural and synthetic products might be α,β-isomers must be considered. The configuration of the natural product is, of course, unknown, although, since the natural purine and pyrimidine ribonucleosides have the β-configuration at the glycosidic carbon atom, one might well expect that the nicotinamide nucleoside would also be a β-compound. We incline to the view that the synthetic riboside we have obtained is, in fact, identical with the natural product on the following grounds. Schlenk and Gingrich (*loc. cit.*) have shown that nicotinamide nucleoside will replace coenzyme-I as a growth factor (V factor) for *Hæmophilus influenzæ* and *H. parainfluenzæ*, an effect not shown by nicotinamide or nicotinic acid. Tests carried out by Mr. D. A. Hughes of Sheffield University have shown that our synthetic dihydronicotinamide-ribofuranoside shows a similar effect, having an activity roughly half that of coenzyme-I on a molar basis.

Experimental.

(Analytical samples were dried *in vacuo* over phosphoric oxide at room temperature for several days. All evaporations under reduced pressure were effected at a bath temperature not exceeding 35°. Light petroleum refers to the fraction of b. p. 40—60°.)

Acetobromo-sugars.—Acetobromo-D-glucopyranose, -D-mannopyranose, -D-galactopyranose, and -L-arabopyranose were all prepared by the following method. The fully acetylated sugar was stirred with twice its weight of a solution of hydrogen bromide in glacial acetic acid (saturated at 0°) for a period of 2 hours, during which time the solid completely dissolved. Chloroform was then added, and the solution poured on ice, separated, and washed with ice-water until the washings were neutral to Congo-red. The chloroform solution was dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The residual syrup was taken up in dry ether, dry light petroleum added to faint cloudiness, and the solution set aside at 0° for some hours. The acetobromo-sugars crystallised in good yield and were sufficiently pure for further work if used within one or two days.

3-*Carbamyl*-2′-*hydroxyethylpyridinium Bromide.*—Ethylene bromohydrin (10 g., 1 mol.) and nicotinamide (10 g., 0·98 mol.) were refluxed in ethanol during 1 hour. The solvent was evaporated, and the residual gum caused to solidify by rubbing it with a few drops of ethanol. The *pyridinium bromide* (17·5 g., 87·5%) was thus obtained as a white crystalline powder, m. p. 141—144°. On recrystallisation from methanol by addition of ethyl acetate the m. p. rose to 148° (Found: C, 39·2; H, 4·5. $C_8H_{11}O_2N_2Br$ requires C, 38·9; H, 4·5%).

3-*Carbamyl*-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* D-*glucopyranosidyl*)*pyridinium Bromide* (cf. Karrer *et al.*, *loc. cit.*).—Acetobromo-D-glucopyranose (15 g.) and nicotinamide (5 g.) were gently refluxed in dry methyl cyanide (70 c.c.) during 3½ hours. A crystalline precipitate separated. The mixture was then set aside overnight and filtered. 3-Carbamyl-N-(2′ : 3′ : 4′ : 6′-tetra-acetyl (?β-)D-glucopyranosidyl)pyridinium bromide (13·78 g., 71%) was thus obtained as a white powder, which crystallised from methanol after the addition of ethyl acetate as colourless plates, m. p. 195—200° (decomp.) (Karrer *et al.*, *loc. cit.*, give m. p. 192—200°, decomp.), $[\alpha]_D^{20}$ −18·3° (*c*, 2·5 in water). The filtrate was evaporated to dryness under reduced pressure; the residue, a dark oil, was taken up in chloroform (30 c.c.) and filtered, and anhydrous ether (150 c.c.) added. A white precipitate separated. This was washed well with ether and dried *in vacuo*. From its analysis and properties this material appeared to be an isomeric 3-*carbamyl*-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* (?α-)D-*glucopyranosidyl*)*pyridinium bromide* (3 g., 15%) (Found: C, 45·3; H, 5·2. $C_{20}H_{25}O_{10}N_2Br$ requires C, 45·1; H, 4·7%), $[\alpha]_D^{20}$ +20·9° (*c*, 2·5 in water).

N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* (?β-)D-*glucopyranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide* (cf. Karrer *et al.*, *loc. cit.*).—A solution of sodium hydrogen carbonate (150 g.) in water (2½ l.) was saturated with carbon dioxide. The crystalline quaternary acetylated glucoside (20 g.) was then added. When this had completely dissolved, sodium dithionite (100 g.) was added. A brilliant yellow colour immediately appeared and there was a vigorous effervescence. The solution was set aside overnight in darkness, during which time a bulky precipitate of matted needles separated. On filtration and washing with water, N-(2′ : 3′ : 4′ : 6′-tetra-acetyl D-glucopyranosidyl)-1 : 2(or 6)-dihydronicotinamide (12·85 g., 75·5%) was obtained as a pale primrose-yellow solid, m. p. 155—157°, which after recrystallisation from water had m. p. 157° (Karrer *et al.*, *loc. cit.*, give m. p. 157—158°), $[\alpha]_D^{20}$ −11·1° (*c*, 0·8 in chloroform).

N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* (?α-)D-*glucopyranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide.*—The non-crystalline quaternary acetylated glucoside (1·85 g.), dissolved in an aqueous solution (200 c.c.) of sodium hydrogen carbonate (20 g.) which had been saturated with carbon dioxide, was treated with sodium dithionite (10 g.). A brilliant yellow colour immediately appeared and there was a vigorous effervescence. The solution was set aside overnight in darkness. No precipitate separated. The solution was extracted several times with chloroform, and the combined extracts washed with water and dried (Na_2SO_4). The chloroform solution was concentrated to small bulk under reduced pressure, and a large excess of dry light petroleum then added. A flocculent yellow precipitate formed. The bulk of the mother-liquor was decanted, and the residue dried *in vacuo*. N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* D-*glucopyranosidyl*)-1 : 2(or 6)-*dihydronicotinamide* (0·70 g., 46%) was thus obtained as a pale-yellow hygroscopic, amorphous powder, easily soluble in most organic solvents, but insoluble in light petroleum (Found: C, 49·9; H, 5·9; N, 5·7. $C_{20}H_{26}O_{12}N_2$ requires C, 52·8; H, 5·8; N, 6·2. $C_{20}H_{26}O_{12}N_2,1\frac{1}{2}H_2O$ requires C, 50·0; H, 6·0; N, 5·8%), $[\alpha]_D^{20}$ +19·9° (*c*, 1·0 in chloroform).

3-*Carbamyl*-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* D-*galactopyranosidyl*)*pyridinium Bromide.*—Acetobromo-D-

galactopyranose (20 g., 1 mol.) and nicotinamide (8·0 g., 1·01 mols.), dissolved in methyl cyanide (100 g.), were kept at 60° during 6 hours and then at room temperature overnight. The solvent was then evaporated under reduced pressure. The residue, a light brown resin, was taken up in cold chloroform, set aside for some hours, and then filtered to remove separated nicotinamide hydrobromide (0·71 g.). The filtrate was evaporated to dryness under reduced pressure. *3-Carbamyl-N-(2′ : 3′ : 4′ : 6′-tetra-acetyl D-galactopyranosidyl)pyridinium bromide* was thus obtained as a very hygroscopic "solid foam," soluble in chloroform, ethanol, and water, but insoluble in ether, ethyl acetate, and light petroleum; it could not be induced to crystallise. For purification, the quaternary salt was redissolved in dry chloroform, the solution filtered, and excess of dry ether added. A flocculent white precipitate formed. The mother-liquors were decanted, and the precipitate was washed 3 times by decantation with dry ether (Found: C, 44·2; H, 4·8; N, 5·2. $C_{20}H_{25}O_{12}N_2Br$ requires C, 45·1; H, 4·7; N, 5·3. $C_{20}H_{25}O_{12}N_2Br,\frac{1}{2}H_2O$ requires C, 44·4; H, 4·8; N, 5·2%). $[\alpha]_D^{18} = +15·2°$ (*c*, 1·2 in water).

3-Carbamyl-N-D-galactopyranosidylpyridinium Bromide.—The quaternary acetylated galactoside (10 g.) was dissolved in water (25 c.c.) containing concentrated hydrobromic acid (0·5 c.c.), and the solution heated in a water-bath at 55—60° for 2 hours. The aqueous solution was evaporated to dryness under reduced pressure to give a colourless gum which was twice evaporated to dryness with ethanol under reduced pressure. The gum was dissolved in a small quantity of dry ethanol, and excess of anhydrous ether added. A precipitate formed which was coagulated by shaking overnight. The precipitate was filtered off and dried in a vacuum-desiccator. *3-Carbamyl-N-D-galactopyranosidylpyridinium bromide* was thus obtained in good yield as a very hygroscopic amorphous powder, very soluble in water and ethanol, sparingly soluble in acetone, and insoluble in chloroform and ether. It retained solvent tenaciously (Found: C, 41·4; H, 5·5; N, 7·1. $C_{12}H_{17}O_6N_2Br,C_2H_5OH$ requires C, 41·0; H, 5·6; N, 6·9%).

N-(2′ : 3′ : 4′ : 6′-Tetra-acetyl D-galactopyranosidyl)-1 : 2(or 6)-dihydronicotinamide.—The quaternary acetylated galactoside (15·9 g.) was dissolved in a saturated aqueous solution (600 c.c.) of sodium hydrogen carbonate which had been saturated with carbon dioxide. Sodium dithionite was added; a brilliant yellow colour immediately appeared and there was a vigorous effervescence. The solution was set aside overnight in darkness. No precipitate separated. The solution was 4 times extracted with chloroform, and the combined extracts washed with water and dried (Na_2SO_4). The chloroform solution was concentrated to small bulk under reduced pressure, and a large excess of dry light petroleum added. A slightly gummy yellow precipitate formed which broke up to a yellow powder on vigorous shaking of the mixture in a mechanical shaker. The mixture was set aside for 14 days, and the precipitate collected. *N-(2′ : 3′ : 4′ : 6′-Tetra-acetyl D-galactopyranosidyl)-1 : 2(or 6)-dihydronicotinamide* (10·45 g., 77%) was obtained as a pale yellow, hygroscopic, amorphous powder, easily soluble in chloroform, ethanol, ethyl acetate, acetone, and methyl cyanide, sparingly soluble in ether and water, and insoluble in light petroleum and benzene. It could not be crystallised and became a glass at *ca.* 60° (Found: C, 53·3; H, 6·3; N, 5·9. $C_{20}H_{28}O_{12}N_2$ requires C, 52·8; H, 5·8; N, 6·2%). $[\alpha]_D^{18} = +10·7°$ (*c*, 2·0 in chloroform).

3-Carbamyl-N-(2′ : 3′ : 4′ : 6′-tetra-acetyl D-mannopyranosidyl)pyridinium Bromide.—Acetobromo-D-mannopyranose (10 g., 1 mol.) and nicotinamide (3·4 g., 1·15 mols.) in methyl cyanide (60 c.c.) were kept at 60° for 7 hours and then at room temperature for 48 hours. The solution was then cooled to 0° and filtered from separated nicotinamide hydrobromide (0·85 g.). Evaporation of the filtrate to dryness under reduced pressure gave *3-carbamyl-N-(2′ : 3′ : 4′ : 6′-tetra-acetyl D-mannopyranosidyl)pyridinium bromide* as a very hygroscopic uncrystallisable foam which was soluble in chloroform, alcohol, and water and insoluble in ether, ethyl acetate, and light petroleum. The material was purified as described for the galactose derivative (Found: C, 44·4; H, 4·8; N, 5·4. $C_{20}H_{25}O_{12}N_2Br$ requires C, 45·1; H, 4·7; N, 5·3. $C_{20}H_{25}O_{12}N_2Br,\frac{1}{2}H_2O$ requires C, 44·4; H, 4·8; N, 5·2%).

N-(2′ : 3′ : 4′ : 6′-Tetra-acetyl D-mannopyranosidyl)-1 : 2(or 6)-dihydronicotinamide.—The quaternary acetylated mannoside (5·47 g.) was dissolved in a saturated aqueous solution (750 c.c.) of sodium hydrogen carbonate which had been saturated with carbon dioxide. Sodium dithionite (25 g.) was added, a brilliant yellow colour immediately developed and there was a brisk effervescence. The solution was set aside in darkness for 24 hours and then extracted with chloroform. The combined extracts were washed with water, and then dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. *N-(2′ : 3′ : 4′ : 6′-Tetra-acetyl D-mannopyranosidyl)-1 : 2(or 6)-dihydronicotinamide* (4·1 g., 88%) separated as a light-yellow hygroscopic solid which could not be crystallised (Found: C, 50·9; H, 5·9; N, 5·6. $C_{20}H_{28}O_{12}N_2$ requires C, 52·8; H, 5·8; N, 6·2. $C_{20}H_{28}O_{12}N_2,H_2O$ requires C, 50·9; H, 5·9; N, 5·9%).

3-Carbamyl-N-(2′ : 3′ : 4′-triacetyl L-arabopyranosidyl)pyridinium Bromide.—Acetobromo-L-arabopyranose (10 g., 1 mol.) and nicotinamide (3·6 g., 1·2 mols.) in methyl cyanide (60 c.c.) were kept at 80° during 5 hours and then overnight at 0°. Separated nicotinamide hydrobromide (1·36 g.) was filtered off, and the solvent evaporated from the filtrate under reduced pressure. The foam so obtained was purified by solution in chloroform and precipitation with ether as previously described. *3-Carbamyl-N-(2′ : 3′ : 4′-triacetyl L-arabopyranosidyl)pyridinium bromide* was obtained as a hygroscopic amorphous powder, very soluble in chloroform, acetone, and water, but insoluble in ether, ethyl acetate, and light petroleum (Found: C, 43·3; H, 4·7; N, 6·0. $C_{17}H_{21}O_9N_2Br$ requires C, 44·3; H, 4·6; N, 6·1. $C_{17}H_{21}O_9N_2Br,\frac{1}{2}H_2O$ requires C, 43·4; H, 4·7; N, 6·0%).

N-(2′ : 3′ : 4′-Triacetyl L-arabopyranosidyl)-1 : 2(or 6)-dihydronicotinamide.—The quaternary acetylated arabinoside (1·25 g.) was reduced with sodium dithionite (5 g.) in sodium hydrogen carbonate solution (100 c.c.) by the procedure previously described. *N-(2′ : 3′ : 4′-Triacetyl L-arabopyranosidyl)-1 : 2(or 6)-dihydronicotinamide* (0·7 g., 86%) was obtained as a light-yellow hygroscopic solid, soluble in ethanol and chloroform, and insoluble in light petroleum; it could not be crystallised (Found: C, 50·7; H, 5·9; N, 6·9. $C_{17}H_{24}O_9N_2$ requires C, 53·5; H, 5·8; N, 7·3. $C_{17}H_{24}O_9N_2,H_2O$ requires C, 50·8; H, 6·0; N, 7·0%).

Dihydronicotinamide Glycosides [N-Glycoside-1 : 2(or 6)-dihydronicotinamides].—General method (*cf.* Karrer *et al.*, *loc. cit.*). The dihydro-acetylated *N*-glycoside was dissolved in methanol (dried by fractionation using a Fenske column), the solution cooled to 0°, saturated at 0° with anhydrous ammonia, and set aside for 24 hours at 0°. The solvent was evaporated under reduced pressure to leave a yellow

solid residue. This was thoroughly extracted with ethyl acetate to remove acetamide, leaving the dihydro-glycoside as a pale yellow, hygroscopic, amorphous powder, which could not, except in the case of the glucoside described by Karrer, be crystallised, and was very readily oxidised when moist. In this way were obtained: *N*-D-glucosidyl-1 : 2(*or* 6)-dihydronicotinamide (93%), m. p. 199° (decomp.), after recrystallisation from water (Karrer *et al.*, *loc. cit.*, give m. p. 203—205°, decomp.), $[\alpha]_D^{18} = +4.9°$ (*c*, 1·5 in water); N-D-*galactopyranosidyl*-1 : 2(or 6)-*dihydronicotinamide* (96%) (Found: C, 48·9; H, 6·8; N, 9·8. $C_{12}H_{18}O_8N_2$ requires C, 50·3; H, 6·3; N, 9·8. $C_{12}H_{18}O_8N_2,H_2O$ requires C, 48·9; H, 6·5; N, 9·5%). $[\alpha]_D^{18} = +30·5°$ (*c*, 2·5 in water); N-D-*mannopyranosidyl*-1 : 2(or 6)-*dihydronicotinamide* (*ca.* 90%) (Found: C, 48·6; H, 6·4; N, 9·0 $C_{12}H_{18}O_8N_2$ requires C, 50·3; H, 6·3; N, 9·8. $C_{12}H_{18}O_8N_2,H_2O$ requires C, 48·9; H, 6·5; N, 9·5); and N-L-*arabopyranosidyl*-1 : 2(or 6)-*dihydronicotinamide* (*ca.* 80%) (Found: C, 50·3; H, 6·5; N, 10·2. $C_{11}H_{16}O_7N_2$ requires C, 51·6; H, 6·3; N, 11·0. $C_{11}H_{16}O_7N_2,H_2O$ requires C, 50·0; H, 6·4; N, 10·6%).

N-(2′ : 3′ : 5′-*Triacetyl* D-*ribofuranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide*.—A solution of aceto-bromo-D-ribofuranose [from tetra-acetyl D-ribofuranose (2·35 g.) (Howard, Lythgoe, and Todd, *J.*, 1947, 1052] in dry methyl cyanide (15 c.c.) was cooled to 0° and added to a solution of nicotinamide (2 g.) in the same solvent (125 c.c.) at 0°. The solution was kept at 0° for 24 hours and then filtered from precipitated nicotinamide hydrobromide (1·0 g.). The filtrate was evaporated to dryness under reduced pressure at room temperature. The residue was dissolved in dry chloroform (15 c.c.), the solution filtered, and excess of anhydrous ether (80 c.c.) added. The precipitated white powder was washed by decantation 3 times with anhydrous ether. On drying *in vacuo* the crude quaternary glycoside (1·4 g.) was obtained as an extremely hygroscopic, amorphous powder. The quaternary salt (1·4 g.) was dissolved in a saturated aqueous solution (175 c.c.) of sodium hydrogen carbonate which had been saturated with carbon dioxide, and the aqueous solution was again saturated with carbon dioxide. Sodium dithionite (6 g.) was then added, a brilliant yellow colour immediately developed and there was a vigorous effervescence. The solution was set aside for 24 hours in darkness and extracted 6 times with chloroform. A nitrogen atmosphere was maintained wherever possible. The combined chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue, a solid foam, was purified by precipitation from chloroform solution with light petroleum. The N-2′ : 3′ : 5′-*triacetyl* D-*ribofuranosidyl*-1 : 2(*or* 6)-*dihydronicotinamide* (0·45 g.) so obtained was a pale yellow, hygroscopic, amorphous solid (Found: C, 52·9; H, 5·9; N, 7·3. $C_{17}H_{22}O_8N_2$ requires C, 53·5; H, 5·8; N, 7·3%), $[\alpha]_D^{18} = -18·3°$ (*c*, 0·8 in chloroform).

N-D-*Ribofuranosidyl*-1 : 2(*or* 6)-*dihydronicotinamide*.—The above acetylated glycoside (0·38 g.) was dissolved in anhydrous methanol (50 c.c.), and the solution cooled to 0°, saturated with anhydrous ammonia, and stored overnight at 0°. The solution was then concentrated under reduced pressure to small bulk, and excess of dry ethyl acetate (70 c.c.) added. The mixture was set aside for several days to age the precipitate, which was then washed thoroughly with dry ethyl acetate to remove acetamide. Filtration gave N-D-*ribofuranosidyl*-1 : 2(*or* 6)-*dihydronicotinamide* as a pale yellow amorphous powder, which could not be crystallised (Found: C, 48·3; H, 6·6; N, 9·7. $C_{11}H_{16}O_6N_2$ requires C, 51·6; H, 6·3; N, 10·9. $C_{11}H_{16}O_6N_2,H_2O$ requires C, 48·3; H, 6·6; N, 10·2%). $[\alpha]_D^{18} = -20·8°$ (*c*, 1·0 in water). The material was very soluble in water, and insoluble in ethyl acetate, light petroleum, ether, and chloroform; it was very hygroscopic and readily oxidised to a dark brown gum when moist.

We are indebted to Messrs. Imperial Chemical Industries Ltd. and Roche Products Ltd. for grants and gifts of material and to Mr. D. A. Hughes for microbiological assays. One of us (L. J. H.) participated in the investigation during his tenure of a D.S.I.R. Senior Research Award and an I.C.I. Fellowship.

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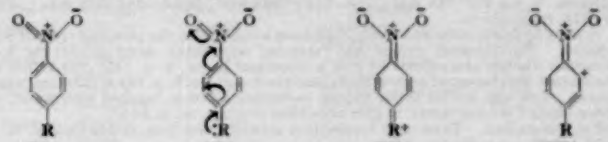
67. *The Magnetic Susceptibility of Certain Organic Compounds. Part III. The Contribution of the Nitro-group to the Magnetic Susceptibility of Aliphatic and Aromatic Nitro-compounds.*

By F. G. BADDAR and S. SUGDEN.

The magnetic susceptibility of certain aromatic and aliphatic nitro-compounds, as well as that of the corresponding parent substances, has been measured in an attempt to determine the contribution of the nitro-group to the magnetic susceptibility of these compounds. Col. 3 in Table III shows that the difference between the magnetic susceptibility of the >C-NO_2 and the >C-H group is highest in the case of *m*-substituted nitro-compounds. This may be due to the fact that resonance leading to structures such as (III) is impossible in these *m*-compounds.

SEVERAL investigators have determined the magnetic susceptibility of the CH_2 group by measuring the susceptibility of a large number of the individuals of a homologous series, *e.g.*, aliphatic acids and their esters (French, *Trans. Faraday Soc.*, 1947, **43**, 356); alcohols, aliphatic acids, and their esters, and aromatic hydrocarbons (Angus and Hill, *ibid.*, 1943, **39**, 190); organic nitrites, nitrates, and nitro-compounds (Gray and Cruickshank, *ibid.*, 1935, **31**, 1491); normal alcohols (Cabrera and Fahlenbrach, *Z. Physik*, 1933, **85**, 568); and acetic acid and its esters (Woodbridge, *Physical Rev.*, 1935, **48**, 672). French (*Trans. Faraday Soc.*, 1945, **41**, 676) measured the susceptibility of certain disubstituted aromatic compounds. She noticed that,

where the substituents are *o*-*p*-directing, the *o*-compounds have a markedly higher diamagnetic susceptibility value than either the *m*- or the *p*-isomerides. When the substituents are *m*-directing, the *m*-compounds have the highest susceptibility. She attributed this to the fact that in compounds containing two electron-repelling groups *ortho* to each other, there is the highest electron density, whereas in compounds containing two electron-attracting groups, the highest electron density is obtained when the two groups are *meta* to each other. However, she noticed that no such regularity could be traced in substituted aromatic nitro-compounds. It is possible that this irregularity may be due to the fact that in these compounds the contribution of the quinonoid structures (cf. III and IV) to the normal state of the molecule (*i.e.*, resonance) is affected by steric hindrance (cf. Birtles and Hampson, *J.*, 1937, 10; Ingham and Hampson, *J.*, 1939, 981) as well as by the position and polar nature of the substituents. Thus, in a molecule like *p*-R·C_6H_4·NO_2, the contribution of the quinonoid structures (III) or (IV) to the actual state of the molecule (or resonance hybrid) is higher if R is an electron-repelling group than if it is an electron-attracting group.



(I.) (II.) (III.) (IV.)

(R = H, CH_3, or NH_2)

In the present investigation the magnetic susceptibility of certain aromatic and aliphatic nitro-compounds as well as of the corresponding parent substances was measured in an attempt to determine the contribution of the nitro-group to the magnetic susceptibility both in aliphatic and in aromatic compounds. To avoid inaccuracy due to unequal packing of solid substances, the measurements for such compounds were carried out in solution, using suitable solvents such as benzene, acetone, and ethyl acetate. The fact that the values of the magnetic susceptibility of the solid, deduced from that of its solutions in any two of these solvents at different concentrations, were found to be identical within the experimental errors, was considered to be a sufficient proof for the validity of the additivity law of solutions (see Table I).

In Table III, col. 3 represents the difference between the magnetic susceptibility of the $>C-NO_2$ group and the $>C-H$ group. The unexpectedly low value ($-4{\cdot}45 \times 10^{-6}$) in the case of *p*-nitroaniline may be due to a solvent effect, whereas that in the case of nitromethane is more difficult to explain. It may be due to the uncertainty in the value of the magnetic susceptibility of methane, which is theoretically deduced (cf. Coulson, *Proc. Physical Soc.*, 1942, **54**, 51; French and Trew, *Trans. Faraday Soc.*, 1945, **41**, 439). It is noticed, however, that in the examples of aromatic nitro-compounds studied (*e.g.*, nitrotoluenes and nitroanilines) the differences in col. 3 of Table III are always highest in case of the *m*-, and lowest in the case of the *p*-derivatives. This may be due to the fact that structures such as (III) are impossible in the case of *m*-substituted nitro-compounds, and although it is possible in the case of the *o*-substituted compounds, yet it may be of less importance owing to steric hindrance (cf. Birtles and Hampson, *loc. cit.*). However, the contribution of the quinonoid structures such as (IV) increases in the case of nitro-compounds substituted by electron-repelling groups in the following order: Unsubstituted nitro-compounds < *m*-nitro- < *o*-nitro- < *p*-nitro-compounds, *i.e.*, nitrobenzene < *m*-nitrotoluene < *o*-nitrotoluene < *p*-nitrotoluene.

Experimental.

The measurements were carried out by the Gouy method using a silica tube which was calibrated by two nickel chloride solutions. Its volume was 25·18 c.c. and its constant (β) was 0·2824 (cf. Baddar, Hilal, and Sugden, *J.*, 1949, 132).

The solid materials used in these measurements were thoroughly purified by repeated crystallisation from pure solvents until a constant value for χ_g was obtained. Similarly, liquid substances were purified by repeated distillation from an all-glass apparatus, the middle fraction always being collected.

Purification of Materials.—Acetone and benzene were purified as stated by Baddar, Hilal, and Sugden (*loc. cit.*).

Ethyl acetate. "AnalaR" Reagent was washed with sodium hydrogen carbonate solution, then with water, and dried over calcium chloride for two weeks. It was fractionally distilled several times, and the fraction, b. p. 76·5—76·6°/756 mm., was collected; $d^{20\cdot0}$ 0·8941.

Toluene. Sulphur-free toluene was shaken with concentrated sulphuric acid, and washed with

water, then with sodium carbonate solution to remove any sulphonated product. It was dried ($CaCl_2$), distilled, shaken several times with mercury, and repeatedly fractionated over sodium; b. p. 110·3—110·4°/768 mm.; $d_4^{20\cdot0}$ 0·8594.

Nitromethane. This was prepared according to *Org. Synth.*, Coll. Vol. I, p. 393; dried ($CaCl_2$), distilled, dried over phosphoric oxide for few hours, and fractionally distilled to give a colourless liquid, b. p. 100—100·4°/752 mm.; $d_4^{24\cdot0}$ 1·131.

2-*Nitropropane.* A sample kindly provided by I.C.I. Ltd. was washed with sodium carbonate solution, dried ($CaCl_2$), and distilled. The drying and distillation were repeated three times. It was finally kept over phosphoric oxide for two hours, decanted, and distilled in a vacuum to give a colourless liquid, b. p. 42°/40 mm., then redistilled at ordinary pressure, b. p. 119·6—120°/763 mm.; $d_4^{24\cdot0}$ 0·9828.

Tetranitromethane. Prepared according to Chattaway (*J.*, 1910, **97**, 2099) and purified by washing with sodium hydrogen carbonate solution (cf. Hammick *et al.*, *J.*, 1936, 1464), this was dried ($CaCl_2$) and distilled in vacuum, b. p. 58—59°/100 mm., then dried over phosphoric oxide for 2 hours, decanted, and distilled; b. p. 47·5—48·5°/40 mm. The product was frozen, and the liquid portion rejected, and the residue then twice distilled; b. p. 46°/36 mm.; $d_4^{24\cdot0}$ 1·6312.

Nitrobenzene and o- *and* m-*nitrotoluene.* A pure sample of each was washed with sodium carbonate solution, then with water, dried ($CaCl_2$), and distilled. It was twice frozen, the liquid portion being rejected, and dried (P_2O_5). By repeated fractional distillation the nitro-compounds were obtained as pale yellow liquids, b. p.s 207°/735 mm., 217—217·1°/738 mm., 228·5—229°/739 mm.; $d_4^{20\cdot0}$ 1·1974, 1·1580, and 1·1524, respectively.

Aniline. Aniline hydrochloride was crystallised from alcohol, and the pure salt treated with sodium hydroxide solution. The liberated aniline was extracted with ether, dried (KOH) for 3 days, and distilled in a carbon dioxide atmosphere to give a colourless liquid, b. p. 183—183·2°/759 mm. The drying and distillation were repeated several times, and the fraction of b. p. 183·4°/759 mm. was collected.

p-*Nitrotoluene.* This was melted under sodium carbonate solution, washed with water, dried, and crystallised from alcohol several times, to give colourless crystals, m. p. 54·5°.

o-, m-, *and* p-*Nitroanaline.* These were crystallised several times from dilute alcohol, m. p.s 71·6—71·8°, 114°, and 148·2°, respectively.

In all cases the measurement was repeated after redistilling or recrystallising the substance. A series of measurements (usually about 6) were then made with the exciting current alternately off and on and the mean reading was taken as the thrust on the specimen. From this was subtracted the thrust on the empty tube (−27·34 mg.), and then $\chi_g \times 10^6$ of the pure liquids was calculated from the formula of Nettleton and Sugden (*Proc. Roy. Soc.*, 1939, *A*, **173**, 313), *viz.*

$$10^6\chi_g = 0{\cdot}29v/w + \beta f/w$$

The meniscus correction, being negligibly small, was neglected.

For solids the magnetic susceptibility was obtained by preparing solutions of different concentrations of the solid substance in suitable solvents of known magnetic susceptibility. By measuring the susceptibility of the solution, and assuming that the additivity law holds for the constituents of the solution, the susceptibility of the solute can be calculated from the equation

$$10^6\chi_{solution} = 10^6\chi_{solute} \times x + 10^6\chi_{solvent}(1 - x), \text{ where } x = \text{concn. of solute in g./g. of solution.}$$

By extrapolation to $x = 1$, the magnetic susceptibility of the solute was obtained.

The measurements were usually carried out in two different solvents, the mean value being taken in each case (see Table I).

To avoid the evaporation of the solvent during the transference of the solution to the specimen tube, the solution was prepared in a small wash-bottle with narrow delivery and pressure tubes closed by stoppers. After the solute and solvent had been weighed into the bottle it was kept in the balance case for ½ hour. The solution was then transferred to the specimen tube by applying a gentle stream of dry air saturated with the vapour of the solvent used.

In Table II sample (*b*) was obtained by redistillation of sample (*a*).

TABLE I.

Substance.	Solvent.	Concn. (x).	No. of detmns.	$-10^6\chi_{sol.}$	$-10^6\chi_g$	$-10^6\chi_g$ (extrap.).	Mean.
o-Nitroaniline	Acetone	0·3362	5	0·5516	0·4943	0·4940	0·4954
,, ...	,,	0·3800	6	0·5477	0·4940		
,, ...	$CH_3{\cdot}CO_2Et$	0·3089	6	0·5795	0·4985	0·4967	
,,	,,	0·2424	6	0·5858	0·4939		
m-Nitroaniline ...	Acetone	0·2156	5	0·5632	0·5000	0·4960	0·4985
,, ...	,,	0·2960	5	0·5547	0·4933		
,, ...	$CH_3{\cdot}CO_2Et$	0·1666	6	0·5966	0·5009	0·5009	
p-Nitroaniline ...	Acetone	0·2046	5	0·5596	0·4769	0·4800	0·4842
,, ...	,,	0·2374	5	0·5581	0·4848		
,, ...	,,	0·2456	4	0·5552	0·4772		
,, ...	,,	0·2594	8	0·5544	0·4798		
,, ...	$CH_3{\cdot}CO_2Et$	0·1109	7	0·6016	0·4882	0·4882	
p-Nitrotoluene ...	Acetone	0·3047	5	0·5632	0·5240	0·5253	0·5257
,, ...	,,	0·3556	6	0·5615	0·5270		
,, ...	Benzene	0·3096	6	0·6477	0·5261	0·5261	
,, ...	,,	0·4112	7	0·6299	0·5263		

TABLE II.

Substance.	$-10^6\chi_A$ (a), mean of 6 readings.	$-10^6\chi_A$ (b), mean of 6 readings.	$-10^6\chi_A$ mean.	$-10^6\chi_M$
Nitromethane	0·3452 ± 0·0004	0·3462 ± 0·0017	0·3457	21·10
2-Nitropropane	0·5131 ± 0·0004	0·5139 ± 0·0005	0·5135	45·73
Tetranitromethane	0·2195 ± 0·0003	—	0·2195	43·02
Nitrobenzene	0·5024 ± 0·0002	0·5026 ± 0·0003	0·5025	61·81
o-Nitrotoluene	0·5272 ± 0·0004	0·5271 ± 0·0009	0·5272	72·28
m-Nitrotoluene	0·5303 ± 0·0003	0·5305 ± 0·0004	0·5304	72·71
Toluene	0·7142 ± 0·0002	0·7157 ± 0·0010	0·7150	65·83
Aniline	0·6701 ± 0·0004	0·6704 ± 0·0006	0·6703	62·37
Ethyl acetate	0·6156 ± 0·0003	0·6155 ± 0·0003	0·6156	54·21

TABLE III.

Substance.	$-10^6\chi_M$.	$-\Delta10^6\chi_M$. ›C·NO$_2$ — ›C·H.	Substance.	$-10^6\chi_M$.	$-\Delta10^6\chi_M$. ›C·NO$_2$ — ›C·H.
Nitrobenzene	61·81 (1)	6·99	Nitromethane	21·10	5·1
Benzene	54·82		Methane	16·00	
o-Nitrotoluene	72·28 (2)	6·45	2-Nitropropane	45·37	6·37
Toluene	65·83		Propane	39·36	
m-Nitrotoluene	72·71 (3)	6·88	Tetranitromethane	43·02	6·75
Toluene	65·83 (4)		Methane	16·00	(27·02)/4
p-Nitrotoluene	72·06 (5)	6·23			
Toluene	65·83				
o-Nitroaniline	68·42 (6)	6·05			
Aniline	62·37				
m-Nitroaniline	68·96 (7)	6·59			
Aniline	62·37				
p-Nitroaniline	66·82 (8)	4·45			
Aniline	62·37 (9)				

(1) Cf. Cabrera and Fahlenbrach, *Z. Physik*, 1934, **89**, 697; Bhatnagar and Mitra, *J. Indian Chem. Soc.*, 1936, **13**, 329; Bhatnagar *et al.*, *ibid.*, p. 273; *Z. Physik*, 1934, **88**, 506. (2) Cf. Bhatnagar, Mathur, and Mal, *Phil. Mag.*, 1930, **10**, 101; Cabrera and Fahlenbrach, *loc. cit.*; Bhatnagar and Mitra, *loc. cit.* (3) Cf. the first two references in (2). (4) Cf. Kido, *Sci. Rep. Tohoku Univ.*, 1936, **24**, 701; Boeker, *Physical Rev.*, 1933, **42**, 756; Angus and Hill, *loc. cit.* (5) Cf. Cabrera and Fahlenbrach, *loc. cit.*; Subramanian, *Proc. Indian Acad. Sci.*, 1936, **3**, *A*, 420; Bose, *Phil. Mag.*, 1936, **21**, 1119. (6) Cf. Bose, *loc. cit.* (7) Cf. Bose, *loc. cit.*; Krishnan and Banerjee, *Phil. Trans.*, 1935, **234**, *A*, 265. (8) Garssen, *Compt. rend.*, 1933, **196**, 541. (9) Cf. Oxley, *Phil. Trans.*, 1914, **214**, *A*, 109; Rao, *Indian J. Physics*, 1934, **8**, 483.

N.B.—(i) $-10^6\chi_M$ for *p*-nitrotoluene, *o*-, *m*-, and *p*-nitroaniline was determined by multiplying the values in the last column of Table I by the corresponding molecular weight.

(ii) The value for propane was derived from that of methane, the magnetic susceptibility increment for the two CH_2 groups being taken as 2 × 11·68 (cf. Angus and Hill, *loc. cit.*).

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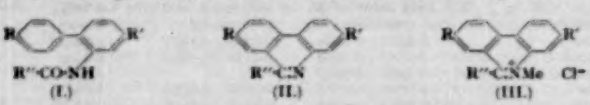
68. *Potential Trypanocides of the* N-*Heterocyclic Series. Part III. Alkoxy- and Hydroxy-phenanthridinium Salts.*

By F. C. COPP and L. P. WALLS.

The observation that a 9-phenylphenanthridinium salt with only methoxyl as substituent possessed significant trypanocidal properties suggested the examination of a series of such compounds and of similar compounds with hydroxyl groups. They were synthesised by conventional methods, and it has emerged that salts with an alkoxyl group in the 7-position are specifically active in *T. congolense* infections, and when in addition the 9-phenyl group has an amino- or a nitro-substituent the activity of some of these substances equals that of the diamino-salts previously described.

A LARGE number of amino-substituted phenanthridinium salts has been prepared (*J.*, 1945, 294; 1947, 67; 1948, 188) and it appeared that the presence of at least one amino-group in the diphenyl portion of the molecule was essential to trypanocidal activity (*Trypanosoma congolense*). This activity is much enhanced by the presence of a 9-phenyl group and of a second amino-group. Compounds which contain amino-groups substituted by acetyl, carbamyl,

or carbalkoxy-groups are found to be much less active against *T. congolense*, although with the last-named modification some activity against the resistant trypanosome, *T. cruzi*, becomes apparent (Walls, Browning, Calver, and Leckie, *Nature*, 1946, **157**, 263; *J.*, 1946, 1031).



Hitherto, the methoxy-group, which is known to exert a favourable therapeutic effect in other series, has not been introduced into the active phenanthridinium types, but its potential value was revealed when *7-methoxy-9-p-methoxyphenyl-10-methylphenanthridinium chloride* (III; R = OMe, R′ = H, R″ = *p*-OMe·C$_6$H$_4$) was found to possess significant trypanocidal activity. The effect of an association of alkoxy- and amino-groups and of hydroxy- and amino-groups was then examined, that type being selected in which the former group was located in the diphenyl portion of the molecule and the latter in the 9-phenyl group. Although compounds with amino-groups restricted to the 9-aryl group had hitherto shown practically no activity, the effect on them of the introduction of a 7-alkoxy-group is striking, many of the compounds now described being powerful trypanocides.

The alkoxy-compounds were prepared by the methods already used in this series, the essential step being the cyclisation of an appropriately substituted *o*-acylamidodiphenyl. *2-Amino-4′-methoxydiphenyl* and its higher homologues were prepared either from 4-amino-2′-acetamidodiphenyl (Petrow, *J.*, 1945, 119) or from 2-nitro-4′-hydroxydiphenyl. The latter substance had been previously prepared by Schultz, Schmidt, and Strasser (*Annalen*, 1881, **207**, 351) who gave only scanty preparative details. Our product had a much lower m. p. (114°) than that recorded by these authors (138°), but its structure was confirmed by its conversion into *2-acetamido-4′-methoxydiphenyl* (I; R = OMe, R′ = H, R″ = Me) and *2-acetamido-4′-(ethyl carbonato)diphenyl* (I; R = O·CO$_2$Et, R′ = H, R″ = Me), identical with the products obtained from 4-amino-2′-acetamidodiphenyl. *2-Nitro-4-methoxydiphenyl* was prepared from 3-nitro-4-aminoanisole and benzene by the Gomberg method, and reduced catalytically to *2-amino-4-methoxydiphenyl*. Condensation of these aminoalkoxydiphenyls with the appropriate acid chlorides yielded the amides (I), which were smoothly cyclised by phosphoryl chloride to the corresponding phenanthridines (II), the latter being readily converted into quaternary salts (III).

The various groups which were introduced into the 9-position are given in detail in the Experimental section (see Tables III, IV, and V); they include methyl, phenyl, phenyl substituted by nitro-, amino-, carbethoxyamino-, methoxy-, hydroxy-, or chloro-groups, and nitro- and amino-benzyl. The 9-aminophenyl compounds were prepared by cyclisation of 2-nitrobenzamidodiphenyls and subsequent reduction of the nitro-group. *2-p-Carbethoxyaminobenzamido-4′-methoxydiphenyl* (I; R = OMe, R′ = H, R″ = *p*-CO$_2$Et·NH·C$_6$H$_4$) was similarly cyclised to the *phenanthridine* (II; R = OMe, R′ = H, R″ = *p*-CO$_2$Et·NH·C$_6$H$_4$) but the corresponding quaternary *salt* could not be converted smoothly into the amino-salt, since the methoxy-group was also affected by the hydrolytic process used.

The preparation of the analogous 9-benzyl compounds (II and III; R = OMe, R′ = H, R″ = *p*-NO$_2$·C$_6$H$_4$·CH$_2$, etc.) presented no difficulty (cf. Part I, *J.*, 1948, 191). The rather low yield of 9-benzylphenanthridine reported by Ritchie (*Proc. Roy. Soc. N. S. Wales*, 1945, **78**, 150) may be attributed to the use of impure 2-phenylacetamidodiphenyl (m. p. 37°); our preparation of this compound (m. p. 85—86°) gave a 68% yield of the phenanthridine. Our results therefore do not support his views on the cyclisation of the phenylacetamido-derivatives. *7-Methoxy-9-p-nitrobenzyl-10-methylphenanthridinium chloride* gave a deep-red product, presumably an anhydro-base, on treatment with water (see Part I).

The hydroxy-phenanthridines or -phenanthridinium salts (III; R or R′ = OH) were best prepared by demethylation of the appropriate methoxy-derivatives with concentrated hydrochloric acid at 160° (Woodruff and Conger, *J. Amer. Chem. Soc.*, 1938, **60**, 405). *7-Hydroxy-9-methylphenanthridine* (II; R = OH, R′ = H, R″ = Me) was thus obtained from the 7-methoxy-compound; it resulted also from the hydrolysis of *7-(ethyl carbonato)*- and *7-benzoyloxy-9-methylphenanthridine* (II; R′ = H, R″ = Me, R = O·CO$_2$Et and OBz, respectively), themselves the products of cyclisation of the corresponding *amides* (I; R′ = H, R″ = Me, R = O·CO$_2$Et and OBz, respectively) but in yields much lower than for the cyclisation of 2-acetamido-4′-methoxydiphenyl (I; R = OMe, R′ = H, R″ = Me). An

attempt to obtain a hydroxyphenanthridine by diazotisation of 7-amino-9-*p*-nitrophenylphenanthridine led only to tars (cf. Part I).

The hydroxyphenanthridines could be alkylated to yield any desired ether, and this method was essential for the preparation of 7-*benzyloxy*-9-p-*nitrophenylphenanthridine*, since attempted ring-closure of 2-p-*nitrobenzamido*-4′-*benzyloxydiphenyl* led to debenzylation and the formation of an intractable resin.

Our colleagues, Dr. Brownlee and Mr. Goodwin, report that most of the quaternary salts prepared as above are powerfully antibacterial *in vitro* and one of them, 7-*methoxy*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium chloride* (III; R = OMe, R′ = H, R″ = *p*-$CO_2Et{\cdot}NH{\cdot}C_6H_4{\cdot}CH_2$), affords protection to mice against *Streptococcus pyogenes*. Certain of them (III; R = alkoxyl, R′ = H, R″ = *p*-$NO_2{\cdot}C_6H_4$ or *p*- or *m*-$NH_2{\cdot}C_6H_4$) possess a powerful curative action for *T. congolense* infections in mice, and consequently it can no longer be postulated that the presence of an amino-group in the diphenyl portion of the molecule is essential to high trypanocidal activity. It is of interest that the toxicity and activity of these salts are much influenced by the length of the *O*-alkyl group, the most active member being 7-*propoxy*-9-p-*aminophenyl*-10-*methylphenanthridinium chloride* (III; R = OPr^n, R′ = H, R″ = *p*-$NH_2{\cdot}C_6H_4$). Although the 2-amino- were more active than the corresponding 7-amino-salts (Part I), the 2-methoxy- were much less active than the 7-methoxy-salts.

Experimental.

2-*Acetamido*-4′-*hydroxydiphenyl*.—4-Amino-2′-acetamidodiphenyl (42 g.) was dissolved in N-sulphuric acid (240 ml.) and diazotised with sodium nitrite (17 g.), more N-sulphuric acid (240 ml.) being added. The diazonium solution was decomposed under toluene. After 48 hours at 0°, the crude 2-*acetamido*-4′-*hydroxydiphenyl* that crystallised from the toluene was collected and dissolved in cold sodium hydroxide solution (charcoal). The filtrate was acidified and the solid thus precipitated crystallised from methanol, forming colourless needles (35 g.), m. p. 185—186° (Found: C, 74·05; H, 5·6. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·8%).

2-*Acetamido*-4′-*methoxydiphenyl*.—A solution of 2-acetamido-4′-hydroxydiphenyl (61 g.) in N-sodium hydroxide (274 ml.) was heated on a steam-bath, and methyl sulphate (29 ml.) added gradually with stirring. After 1 hour the mixture was cooled, the resulting solid taken up into ether, and the ethereal solution washed with N-sodium hydroxide and dried. Evaporation of the ether left 2-*acetamido*-4′-*methoxydiphenyl*, b. p. 130°/0·01 mm. (50 g.). The colourless distillate crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in plates, m. p. 134° (Found: C, 75·1; H, 6·3. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2%).

The following 2-acetamido-4′-alkoxydiphenyls were similarly prepared: 4′-*Ethoxy*-, b. p. 135°/0·01 mm., crystallised from aqueous *iso*propanol, m. p. 91° (Found: C, 75·1; H, 6·75. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7%). 4′-*iso*Propoxy-, crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 108—109·5° (Found: C, 75·9; H, 7·1. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 6·95%). 4′-*n*-*Butoxy*-, b. p. 155°/1 × 10^{-3} mm., crystallised from ether–light petroleum (b. p. 40—60°), m. p. 98° (Found: C, 76·6; H, 7·4; N, 4·8. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5; N, 4·9%). 4′-*Benzyloxy*-, b. p. 190—200°/1 × 10^{-3} mm., crystallised from ethyl acetate, m. p. 138° (Found: C, 79·6; H, 5·8. $C_{21}H_{19}O_2N$ requires C, 79·5; H, 6·0%). 4′-(*Ethyl carbonato*)-, prepared from an alkaline solution of 2-acetamido-4′-hydroxydiphenyl and ethyl chloroformate, and crystallised from ethanol in colourless needles, m. p. 127—128° (Found: C, 68·2; H, 5·8. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7%). 4′-*Benzoyloxy*-, prepared by the Schotten–Baumann method, crystallised from methanol, m. p. 187—188° (Found: N, 4·4. $C_{21}H_{17}O_3N$ requires N, 4·2%).

2-*Nitro*-4′-*hydroxydiphenyl*.—A solution of 2-nitro-4′-aminodiphenyl (35·2 g.) in boiling N-sulphuric acid (640 ml.) was rapidly cooled to produce a fine paste, which was diazotised with sodium nitrite (9·5 g.). The diazonium solution was decomposed under toluene, which extracted the phenol as it was formed. After cooling, the toluene layer was extracted with aqueous sodium hydroxide, the phenol regenerated, and then crystallised from trichloroethylene as brownish crystals (22 g.), m. p. 110—112°, pure enough for the next stage. Its further purification was effected by percolating a benzene solution through a short column of alumina and extracting the filtrate with aqueous sodium hydroxide. The regenerated product now crystallised from trichloroethylene in lemon-coloured prisms, m. p. 114° (Found: C, 66·8; H, 4·3; N, 6·9. Calc. for $C_{12}H_9O_3N$: C, 67·0; H, 4·2; N, 6·5%).

From this product were prepared the *acetate*, m. p. 122° (Found: C, 65·6; H, 4·3. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%), *methyl ether*, m. p. 60—60·5° (Found: C, 68·0; H, 5·1; N, 6·1. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%), *ethyl ether*, m. p. 51° (Found: C, 69·2; H, 5·3. $C_{14}H_{13}O_3N$ requires C, 69·2; H, 5·4%), and *ethyl carbonate*, m. p. 121° (Found: C, 62·5; H, 4·4. $C_{15}H_{13}O_5N$ requires C, 62·4; H, 4·5%).

2-*Amino*-4′-*methoxydiphenyl*.—This was obtained in almost quantitative yield by catalytic reduction (5% palladium–charcoal) of 2-nitro-4′-methoxydiphenyl at 70° with hydrogen (50 atm.). The *amine* was an oil, b. p. 118—120°/0·1 mm., which, subsequently solidified, had m. p. 36° (Found: C, 78·4; H, 6·8. $C_{13}H_{13}ON$ requires C, 79·4; H, 6·6%); its *hydrochloride* crystallised from 2N-hydrochloric acid in colourless needles, m. p. 227—228° (Found: C, 66·6; H, 6·4. $C_{13}H_{14}ONCl$ requires C, 66·4; H, 6·0%). Acetylation of the base with acetic anhydride gave 2-acetamido-4′-methoxydiphenyl identical with the product prepared from 4-amino-2′-acetamidodiphenyl as already described. By similar processes were prepared 2-*amino*-4′-*ethoxydiphenyl*, b. p. 130—135°/0·1 mm., m. p. 56° (Found: C, 79·1; H, 7·1; OEt, 20·9. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1; OEt, 21·1%), and 2-*amino*-4′-(*ethyl*

carbonate)diphenyl, which crystallised from *cyclo*hexane in colourless prisms, m. p. 65—66° (Found: C, 70·3; H, 5·9. $C_{18}H_{19}O_4N$ requires C, 70·0; H, 5·8%). Acetylation of the latter gave 2-acetamido-4'-(ethyl carbonato)diphenyl, identical with that previously described.

TABLE I.

o-Acylamidodiphenyls (I).

Diphenyls.	Solvent for recrystn.	M. p.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
2-*Benzamido*-4'-*methoxy*-	Methanol	108°	$C_{20}H_{17}O_2N$	79·1	5·5	4·8	79·2	5·6	4·6
2-*Anisamido*-4'-*methoxy*-	Acetone	146	$C_{21}H_{19}O_3N$	76·0	5·7	—	75·6	5·9	—
2-p-*Chlorobenzamido*-4'-*methoxy*-	Ethanol	142—143	$C_{20}H_{16}O_2NCl$	(Cl, 10·6)		4·1	(Cl, 10·5)		4·1
2-p-*Nitrobenzamido*-4'-*methoxy*-	Ethanol	164—165	$C_{20}H_{16}O_4N_2$	69·0	4·55	8·3	69·0	4·6	8·1
2-m-*Nitrobenzamido*-4'-*methoxy*-	Ethanol	136·5—137	„	69·1	4·8	8·4	„	„	„
2-p-*Carbethoxyamino*-*benzamido*-4'-*methoxy*-	Methanol	178	$C_{23}H_{24}O_4N_2$	70·8	5·9	7·4	70·75	5·7	7·2
2-(3 : 5-*Dinitrobenz*-*amido*)-4'-*methoxy*-	Acetic acid	179—180·5	$C_{20}H_{15}O_6N_3$	61·5	3·9	10·4	61·1	3·8	10·6
2-p-*Nitrobenzamido*-4'-*ethoxy*-	Ethanol	147	$C_{21}H_{18}O_4N_2$	—	—	7·9	—	—	7·7
2-p-*Nitrobenzamido*-4'-*isopropoxy*-	Ethanol	139	$C_{22}H_{20}O_4N_2$	69·9	5·2	7·5	70·2	5·4	7·4
2-p-*Nitrobenzamido*-4'-*n-butoxy*-	Ethanol	118	$C_{23}H_{22}O_4N_2$	—	—	7·2	—	—	7·2
2-p-*Nitrobenzamido*-4'-*benzyloxy*-	Ethyl acetate	146—147	$C_{27}H_{22}O_4N_2$	73·6	4·7	6·3	73·6	4·7	6·6
2-p-*Nitrobenzamido*-4'-*methoxy*-	Benzene	170	$C_{20}H_{16}O_4N_2$	—	—	8·0	—	—	8·1
2-*Phenylacetamido*-	*cyclo*Hexane	85—86	$C_{20}H_{17}ON$	83·2	6·1	5·1	83·6	5·95	4·9
2-p-*Methoxyphenyl*-*acetamido*-	*cyclo*Hexane	105	$C_{21}H_{19}O_2N$	79·7	6·2	4·7	79·5	6·0	4·4
2-p-*Nitrophenyl*-*acetamido*-4'-*methoxy*-	Benzene	149—150	$C_{21}H_{18}O_4N_2$	—	—	8·0	—	—	7·7

Alternatively, 2-acetamido-4'-methoxydiphenyl (50 g.) (prepared as previously described, from 4-amino-2'-acetamidodiphenyl) was dissolved in a mixture of concentrated sulphuric acid (24 ml.) and ethanol (450 ml.), and the mixture refluxed for 1½ hours. After neutralisation with ammonia the solution was evaporated under reduced pressure, the residue treated with excess of ammonia, and the precipitated oil extracted with ether. The ethereal solution was washed with water, dried, and evaporated; distillation of the residue gave 2-amino-4'-methoxydiphenyl (31 g.). By analogous processes were prepared: 2-amino-4'-ethoxydiphenyl, 2-*amino*-4'-*isopropoxydiphenyl*, b. p. 128—134°/0·05 mm. (Found: N, 6·3. $C_{15}H_{17}ON$ requires N, 6·2%), 2-*amino*-4'-*n-butoxydiphenyl*, b. p. 140°/0·003 mm. (Found: C, 79·6; H, 7·7; N, 6·1. $C_{16}H_{19}ON$ requires C, 79·65; H, 7·9; N, 5·8%), and 2-*amino*-4'-*benzyloxydiphenyl* which, crystallised directly from ethanol, had m. p. 122° (Found: N, 5·15. $C_{19}H_{17}ON$ requires N, 5·1%).

2-*Nitro*-4-*methoxydiphenyl*.—3-Nitro-4-aminoanisole (150 g.) (Fanter and Tarbell, *Org. Synth.*, **25**, 78) was dissolved in hot 10*N*-hydrochloric acid (280 ml.) with just enough water (75 ml.) to give a clear solution, which was cooled to 0° and diazotised with sodium nitrite (67·5 g.). It was then stirred vigorously with benzene (2 l.) at 5—10° and sodium acetate (300 g.) in concentrated aqueous solution added. After 48 hours the benzene layer was separated and washed with alkali, whereupon a thick tar separated; the benzene layer was decanted, washed with fresh alkali, and finally with water. The residue left after evaporation of the benzene was exhaustively extracted with boiling ether, the combined extracts were evaporated, and the residue was distilled in a vacuum. 2-*Nitro*-4-*methoxydiphenyl*, b. p. 120—135°/0·05 mm., subsequently solidified, and crystallised from carbon tetrachloride–light petroleum (b. p. 40—60°) as pale yellow needles, m. p. 75—77° (Found: C, 68·4; H, 4·5; N, 6·35. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%).

2-*Amino*-4-*methoxydiphenyl*.—A solution of 2-nitro-4-methoxydiphenyl in ethanol (250 ml.) was reduced over palladium–charcoal (4 g. of 5%) at 40—60° with hydrogen (50 atm.). The *amine* was an oil, b. p. 128—130°/0·06 mm. (Found: C, 78·4; H, 6·8; N, 7·2. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%).

p-*Carbethoxyaminobenzoic Acid*.—This acid has been described by Boehm and Mehta (*Ber.*, 1938, **71**, 1797) but their method has little preparative value. This acid is readily obtained by the action of ethyl chloroformate on an alcoholic solution of *p*-aminobenzoic acid in the presence of an equivalent of diethylaniline, or, alternatively, by the action of excess of this ester on an aqueous solution of the hydrochloride of *p*-aminobenzoic acid. The product crystallised from methanol in colourless needles,

TABLE II.

Phenanthridines (II).

Phenanthridines.	Solvent for recrystn.	M. p.	Yield, %.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
7-*Methoxy*-9-*methyl*-	Distilled, b. p. 141—148°/0·003 mm.	57°	60	$C_{15}H_{15}ON$	80·4	5·8	6·4	80·7	5·9	6·3
7-(*Ethyl carbonato*)-9-*methyl*-	*cyclo*Hexane	98—99	Variable	$C_{17}H_{15}O_2N$	72·6	5·5	—	72·6	5·4	—
7-(*Ethyl carbonato*)-9-*methyl*-, HCl	Ethanol	205—206	—	$C_{17}H_{16}O_2NCl$	64·4	5·4	—	64·2	5·1	—
7-*Benzoyloxy*-9-*methyl*-	Benzene	208—209	20	$C_{21}H_{15}O_2N$	80·7	4·75	4·5	80·5	4·8	4·5
7-*Methoxy*-9-*phenyl*-	Distilled, b. p. 190—192°/0·01 mm.	Gum	67	$C_{20}H_{15}ON$	—	—	4·7	—	—	4·9
7-*Methoxy*-9-*phenyl*-, *picrate*	Acetic acid	270—271	—	$C_{26}H_{18}O_8N_4$	—	—	10·75	—	—	10·9
7-*Methoxy*-9-*p-methoxyphenyl*-	Light petroleum (b. p. 80—100°)	94	80	$C_{21}H_{17}O_2N$	79·9	5·6	—	80·0	5·4	—
7-*Methoxy*-9-*p-chlorophenyl*-	Benzene and light petroleum (b. p. 80—100°)	157—158	73	$C_{20}H_{14}ONCl$	75·1	4·1	4·3	75·1	4·4	4·4
7-*Methoxy*-9-*p-nitrophenyl*-	Benzene	233—234	72	$C_{20}H_{14}O_3N_2$	72·6	4·3	8·4	72·7	4·3	8·5
7-*Methoxy*-9-*m-nitrophenyl*-	Benzene	183—184	81	,,	73·0	4·4	8·4	,,	,,	,,
7-*Methoxy*-9-*p-carbethoxyamino-phenyl*-	Benzene	132—136	70	$C_{23}H_{23}O_4N_3,0{\cdot}5H_2O$	72·2	5·35	—	72·4	5·5	—
7-*Methoxy*-9-(3 : 5-*dinitrophenyl*)-	Pyridine	252—253	57	$C_{20}H_{13}O_5N_3$	—	—	11·1	—	—	11·2
7-*Ethoxy*-9-*p-nitrophenyl*-	Chloroform	233	60	$C_{21}H_{16}O_3N_2$	—	—	8·1	—	—	8·1
* 7-n-*Propoxy*-9-*p-nitrophenyl*-	Ethanol	169	60	$C_{23}H_{18}O_3N_2$	74·0	5·3	7·65	73·7	5·1	7·6
* 7-n-*Propoxy*-9-*m-nitrophenyl*-	Ethanol	146	60	,,	—	—	7·8	—	—	,,
7-*iso*Propoxy-9-*p-nitrophenyl*-	Ethanol	159—160	60	,,	74·1	5·2	7·9	73·7	5·1	,,
7-n-*Butoxy*-9-*p-nitrophenyl*-	Benzene	173	67	$C_{24}H_{20}O_3N_2$	—	—	7·6	—	—	7·5
* 7-*Benzyloxy*-9-*p-nitrophenyl*-	*n*-Propanol	180	70	$C_{26}H_{18}O_3N_2$	76·5	4·1	7·0	76·85	4·4	6·9
3-*Methoxy*-9-*p-nitrophenyl*-	Benzene	199	90	$C_{20}H_{14}O_3N_2$	—	—	8·3	—	—	8·5
9-Benzyl-	Ethanol	111—112	68	—	—	—	—	—	—	—
9-*p-Methoxybenzyl*-	Ethanol	125—127	70	$C_{21}H_{17}ON$	84·2	5·75	—	84·3	5·7	—
7-*Methoxy*-9-*p-nitrobenzyl*-	Toluene	142	93	$C_{21}H_{16}O_3N_2$	—	—	8·1	—	—	8·1
† 7-*Hydroxy*-9-*methyl*-	Nitrobenzene	298—300	95	$C_{14}H_{11}ON$	79·8	5·2	—	80·3	5·3	—
† 7-*Hydroxy*-9-*methyl*-, HCl	Water	285—287	—	$C_{14}H_{12}ONCl$	68·9	5·2	—	68·4	4·9	—
7-*Hydroxy*-9-*p-nitrophenyl*-	Acetic acid	275	80	$C_{19}H_{12}O_3N_2$	—	—	8·7	—	—	8·9
7-*Hydroxy*-9-*m-nitrophenyl*-	*iso*Propanol	250	75	,,	—	—	8·6	—	—	,,

* Prepared by alkylation of the appropriate 7-hydroxyphenanthridine.

† Prepared by alkaline hydrolysis of 7-(ethyl carbonato)-9-methylphenanthridine as well as by demethylation of 7-methoxy-9-methylphenanthridine.

m. p. 203° (Found: N, 6·9. Calc. for $C_{20}H_{21}O_4N$: N, 6·7%). It was converted into *p-carbethoxyaminobenzoyl chloride* by hot thionyl chloride; white needles, m. p. 110°, separated from benzene. (Found: N, 6·6; Cl, 15·6. $C_{11}H_{10}O_3NCl$ requires N, 6·15; Cl, 15·6%).

o-Acylamidodiphenyls.—The amides (Table I) were (with one exception) prepared by the following method. To a solution of the appropriate 2-amino-4′-alkoxydiphenyl (0·1 mole) in chloroform (200 ml.), anhydrous sodium carbonate (10 g.) was added, followed by the appropriate acid chloride (10% excess). The mixture was stirred for 30 minutes and then heated under reflux for a further 30 minutes. The hot solution was filtered, and the insoluble residue washed with warm chloroform. The combined filtrate and washings were evaporated to give the crude amide. *p*-Carbethoxyaminobenzoyl chloride and 2-amino-4′-methoxydiphenyl were condensed in boiling chlorobenzene.

Table III.

Alkoxy-10-*methylphenanthridinium salts* (III; R or R′ = alkoxyl).

(Chlorides, except where otherwise stated. All salts in this and succeeding tables were dried at 100° before analysis.)

Phenanthridinium salts.	Solvent for crystn.	M. p.	Formula.	Analysis. Found, %. N.	Cl.	Required, %. N.	Cl.
7-*Methoxy*-9-*methyl*- (*bromide*)	Water	238°	$C_{14}H_{14}ONBr$	(Br, 24·7)		(Br, 25·1)	
7-*Methoxy*-9-*phenyl*-	PrⁱOH and Et_2O	216—217	$C_{20}H_{16}ONCl$	4·35	10·6	4·2	10·55
7-*Methoxy*-9-p-*methoxyphenyl*-	"	215—216	$C_{21}H_{18}O_2NCl$	4·0	—	3·8	—
7-*Methoxy*-9-p-*chlorophenyl*-	Water	229—230	$C_{20}H_{15}ONCl_2$	"	19·1	"	19·2
7-*Methoxy*-9-p-*nitrophenyl*-	Dil. HCl	230—232	$C_{20}H_{15}O_3N_2Cl$	—	9·6	—	9·3
7-*Methoxy*-9-p-*aminophenyl*-	*iso*Propanol	253—254	$C_{20}H_{17}ON_2Cl$	—	10·3	—	10·1
7-*Methoxy*-9-p-*acetamidophenyl*-	Ethanol	258—259	$C_{22}H_{19}O_2N_2Cl$	7·3	—	7·1	—
7-*Methoxy*-9-p-*carbethoxyaminophenyl*-	Ethanol	248—249	$C_{23}H_{21}O_3N_2Cl$	6·7	8·3	6·6	8·4
7-*Methoxy*-9-m-*nitrophenyl*-	Dil. HCl	229	$C_{20}H_{15}O_3N_2Cl$	7·3	—	7·4	—
7-*Methoxy*-9-m-*aminophenyl*-	Water	236—238	$C_{20}H_{17}ON_2Cl$	—	10·2	—	10·1
7-*Methoxy*-9-m-*carbethoxyaminophenyl*-	EtOH and Et_2O	232—233	$C_{23}H_{21}O_3N_2Cl$	6·9	9·35	6·6	8·4
7-*Methoxy*-9-(3 : 5-*dinitrophenyl*)-	Water	260	$C_{20}H_{14}O_5N_3Cl$	10·0	8·6	9·9	8·3
7-*Methoxy*-9-(3 : 5-*diaminophenyl*)-	Ethanol	252—253	$C_{20}H_{19}ON_3Cl$	11·8	9·9	11·5	9·7
7-*Ethoxy*-9-p-*nitrophenyl*-	Dil. HCl	233	$C_{21}H_{17}O_3N_2Cl$	6·95	9·0	7·1	9·0
7-*Ethoxy*-9-p-*aminophenyl*-	Ethanol	225—226	$C_{21}H_{19}ON_2Cl$	7·6	9·6	7·7	9·7
7-n-*Propoxy*-9-p-*nitrophenyl*-	Dil. HCl	222	$C_{22}H_{19}O_3N_2Cl$	6·5	8·6	6·85	8·7
7-n-*Propoxy*-9-p-*aminophenyl*-	*iso*Propanol	215	$C_{22}H_{21}ON_2Cl$	—	9·5	—	9·4
7-n-*Propoxy*-9-m-*nitrophenyl*-	*iso*Propanol	212	$C_{22}H_{19}O_3N_2Cl$	—	8·4	—	8·7
7-n-*Propoxy*-9-m-*aminophenyl*-	Water	206	$C_{22}H_{21}ON_2Cl$	7·6	9·0	7·4	9·4
7-n-*Propoxy*-9-m-*carbethoxyaminophenyl*-	*iso*Propanol	207	$C_{25}H_{27}O_3N_2Cl$	6·5	8·2	6·2	7·9
7-*iso*Propoxy-9-p-*nitrophenyl*-	Dil. HCl	239—240	$C_{22}H_{19}O_3N_2Cl$	6·8	8·9	6·85	8·7
7-*iso*Propoxy-9-p-*aminophenyl*- (*dihydrate*)	Water	174—175	$C_{22}H_{23}ON_2Cl$	7·4	9·6	7·4	9·4
7-n-*Butoxy*-9-p-*nitrophenyl*-	Water	234	$C_{23}H_{21}O_3N_2Cl$	6·7	8·8	6·6	8·4
7-n-*Butoxy*-9-p-*aminophenyl*-	*iso*Propanol	190	$C_{23}H_{23}ON_2Cl$	7·3	9·1	7·1	9·0
7-*Benzyloxy*-9-p-*nitrophenyl*-	Water	226	$C_{27}H_{21}O_3N_2Cl$	6·2	7·9	6·2	7·9
7-*Benzyloxy*-9-p-*aminophenyl*-	Dil. EtOH	184	$C_{27}H_{23}ON_2Cl$	6·2	8·3	6·6	8·3
2-*Methoxy*-9-p-*nitrophenyl*-	Methanol	234	$C_{21}H_{17}O_3N_2Cl$	7·2	9·1	7·4	9·3
2-*Methoxy*-9-p-*aminophenyl*-	Water	235	$C_{21}H_{19}ON_2Cl$	8·1	—	8·0	—

Phenanthridines and Phenanthridinium Salts.—These compounds (Tables II—V) were prepared by the following general methods. The *o*-acylamidodiphenyl was suspended in phosphoryl chloride (1 ml. to 1 g. of amide), and the mixture refluxed for 5 hours, and then decomposed with ice and water. The resulting solid was ground with a mixture of chloroform and concentrated hydrochloric acid, and the insoluble residue collected and washed with a little fresh chloroform and hydrochloric acid. Unchanged starting material was recovered from the chloroform solution. The chloroform-insoluble material, on being treated with aqueous ammonia, gave the almost pure phenanthridine. After recrystallisation from the appropriate solvent, the phenanthridine was treated with excess of methyl sulphate in nitrobenzene at 150° for 15 minutes. After cooling, the nitrobenzene was removed in steam, and the residual product extracted with hot water. The methochlorides were precipitated from the extract with concentrated hydrochloric acid. The aminophenanthridinium salts were prepared by reduction of the corresponding nitrophenanthridinium salts with a small excess of iron powder or a sludge of ferrous hydroxide. Demethylation of methoxyphenanthridines or methoxyphenanthridinium salts was effected by heating the starting material with excess of concentrated hydrochloric acid in a sealed tube at 160—170° for 3 hours. With cooling, the hydrochloride or chloride was collected, and the former basified to give the corresponding hydroxyphenanthridine.

Alkylation of Hydroxyphenanthridines.—The appropriate hydroxyphenanthridine was dissolved in an equivalent amount of sodium hydroxide solution and the solution stirred in an oil-bath at 120°

together with an excess (50%) of the appropriate alkyl iodide (or benzyl chloride). The reaction was slow and usually took about 12 hours for completion. The precipitated solid was collected, washed with water, and extracted with hot aqueous sodium hydroxide to remove unchanged starting material. The residue was then crystallised from the appropriate solvent.

TABLE IV.

Hydroxy-10-*methylphenanthridinium chlorides* (III; R or R′ = OH).

Phenanthridinium salts.	Solvent for crystn.	M. p. (decomp.).	Formula.	Analysis. Found, %. N.	Found, %. Cl.	Required, %. N.	Required, %. Cl.
7-*Hydroxy*-9-*methyl*-	Methanol	262—263°	$C_{14}H_{14}ONCl$	5·4	13·6	5·4	13·6
7-*Hydroxy*-9-*phenyl*-	Water	263—264	$C_{19}H_{16}ONCl$	4·3	11·4	4·35	11·0
7-*Hydroxy*-9-p-*hydroxyphenyl*-	Aq. alcohol	264—265	$C_{19}H_{16}O_2NCl$	4·5	—	4·15	—
7-*Hydroxy*-9-p-*chlorophenyl*-	Dil. HCl	244—245	$C_{19}H_{15}ONCl_2$	4·0	20·0	3·9	19·9
7-*Hydroxy*-9-p-*nitrophenyl*-	Methanol	252	$C_{19}H_{15}O_3N_2Cl$	7·6	9·4	7·6	9·7
7-*Hydroxy*-9-p-*aminophenyl*-	Water	269—271	$C_{19}H_{17}ON_2Cl$	8·45	10·8	8·3	10·5
7-*Hydroxy*-9-p-*carbethoxy-aminophenyl*-	Methanol	281—282	$C_{22}H_{21}O_3N_2Cl$	7·1	—	6·7	—
7-*Hydroxy*-9-m-*aminophenyl*-	Water	275—277	$C_{19}H_{17}ON_2Cl$	8·6	10·4	8·3	10·5
7-*Hydroxy*-9-m-*carbethoxy-aminophenyl*-	Ethanol	198—200	$C_{22}H_{21}O_3N_2Cl$	(OEt, 11·5)	8·9	(OEt, 11·0)	8·7
2-*Hydroxy*-9-p-*nitrophenyl*-	Water	330	$C_{19}H_{15}O_3N_2Cl$	7·4	9·6	7·6	9·7
2-*Hydroxy*-9-p-*aminophenyl*-	Water	297—298	$C_{19}H_{17}ON_2Cl$	8·4	10·35	8·3	10·5

TABLE V.

9-*Benzyl*-10-*methylphenanthridinium chlorides* (III; R″ = benzyl).

Phenanthridinium salts.	Solvent for crystn.	M. p. (decomp.).	Formula.	Analysis. Found, %. N.	Found, %. Cl.	Required, %. N.	Required, %. Cl.
9-*Benzyl*-	*iso*Propanol	205—207°	$C_{21}H_{18}NCl$	4·6	—	4·4	—
9-p-*Methoxybenzyl*-	*iso*Propanol	192	$C_{22}H_{20}ONCl$	—	9·8	—	10·1
7-*Methoxy*-9-p-*nitrobenzyl*-	Methanol	151	$C_{22}H_{19}O_3N_2Cl$	7·0	—	7·1	—
7-*Methoxy*-9-p-*aminobenzyl*-	Water	241	$C_{22}H_{21}ON_2Cl$	7·4	9·5	7·7	9·7
7-*Methoxy*-9-p-*carbethoxy-aminobenzyl*-	Ethanol	220	$C_{25}H_{25}O_3N_2Cl$	6·5	8·0	6·4	8·1
7-*Methoxy*-9-p-*propionamido-benzyl*-	Water	218	$C_{25}H_{25}O_3N_2Cl$	6·6	8·0	6·6	8·4
7-*Hydroxy*-9-p-*aminobenzyl*-	Water	252	$C_{21}H_{19}ON_2Cl$	7·8	10·0	8·0	10·1
7-*Hydroxy*-9-p-*carbethoxy-aminobenzyl*-	Dil. HCl	265	$C_{24}H_{23}O_3N_2Cl$	6·8	—	6·6	—

The phenanthridines are colourless or very pale yellow solids. The phenanthridinium salts are light yellow, except those with a 9-*p*-aminophenyl substituent which are bright red, and the 9-*m*-aminophenyl analogues which are very deep orange.

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69. *The Reactions of Propylene Sulphide with Acetyl Chloride and Related Compounds.*

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Acetyl chloride and propylene sulphide rapidly form 2-chloropropyl thiolacetate (II). Acetyl bromide behaves similarly, but acetic anhydride in the presence of pyridine gives 2-*acetylthiopropyl acetate* (X). These esters are converted into the corresponding mercaptopropanols, of which the structures have been proved by the properties of their crystalline derivatives. The two mercaptopropanols are converted by aqueous hydrochloric acid into the same chloropropanethiol [considered to be 2-chloropropane-1-thiol (IX)], which is also formed by the interaction of propylene sulphide and aqueous hydrochloric acid.

THE usual or "normal" interaction of compounds containing active hydrogen with asymmetrical ethylene oxides is to form derivatives of secondary alcohols, and the rare fission of asymmetrical

ethylene oxides to form derivatives of primary alcohols is regarded as the abnormal process (Kadesch, *J. Amer. Chem. Soc.*, 1946, **68**, 41; Chitwood and Freure, *ibid.*, p. 680; Gilman and Fullhart, *ibid.*, 1949, **61**, 1478). This use of the terms " normal " and " abnormal " is adopted in the present paper with reference to the fission of ethylene sulphides to form secondary or primary thiols, respectively, or derivatives of them. Thus the conversion of propylene sulphide (I) into the derivative (X) of propane-2-thiol results from normal ring fission, as the sulphur atom retains its link with $C_{(2)}$.

Propylene sulphide (I) reacts spontaneously with acetyl chloride to give 2-chloropropyl thiolacetate (II) in theoretical yield. This abnormal product shows no evidence of being a mixture of isomers. The compound (II) has already been described by Culvenor, Davies, and Heath (*J.*, 1949, 286), but its structure has not been proved. Its conversion into known crystalline derivatives is difficult, for it is inert to sodium iodide in boiling acetone, and is converted by zinc and acetic acid into viscous material; Raney nickel removes both sulphur and chlorine, and concentrated nitric acid gives an almost theoretical yield of sulphuric acid together with a small amount of oxalic acid. However, (II) is converted by potassium acetate in glacial acetic acid into 1-*acetylthio*-2-*propyl acetate* (III), which is hydrolysed by 1% methanolic hydrochloric acid to 1-mercaptopropan-2-ol (IV), a liquid characterised as the *derivative* (V) (obtained by interaction with 2 moles of phenyl *iso*cyanate) and as the 2 : 4 : 6-*trinitrophenyl thioether* (VI; R = picryl). The structure of (IV) is shown by its reaction with 1-chloro-2 : 4-dinitrobenzene and alkali to form 1-(2 : 4-*dinitrophenylthio*)*propan*-2-*ol* [VI; R = 2 : 4-$(NO_2)_2C_6H_3$], also obtained from 2 : 4-dinitrothiophenol and 1-bromopropan-2-ol and oxidised by chromic acid to (2 : 4-*dinitrophenylthio*) *acetone* (VII), which is identical with the reaction product from bromoacetone and 2 : 4-dinitrothiophenol.

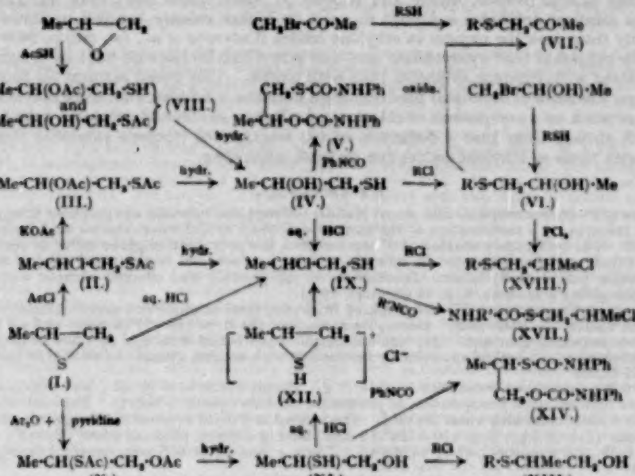
This proof of the structure of (IV) is independent of previous work, and depends on evidence supplied by the properties of the 2 : 4-dinitrophenyl derivative. Sjöberg (*Ber.*, 1942, **75**, *B*, 27) found that propylene oxide and thiolacetic acid, $CH_3{\cdot}CO{\cdot}SH$, formed a mixture (VIII) of 1-acetylthiopropan-2-ol and 2-acetoxypropane-1-thiol, which gave (IV) on hydrolysis. These formulæ seem to have been assumed by Sjöberg by analogy with the products from glycidol and thiolacetic acid. A repetition of his work confirms his formula (IV), and thus proves that the reaction of propylene oxide with thiolacetic acid is a normal one.

Propylene sulphide reacts abnormally with acetyl bromide, and the apparently homogeneous 2-*bromopropyl thiolacetate* (over 95% yield) is converted into (III) by sodium acetate in glacial acetic acid. By analogy, the product from benzoyl chloride (Culvenor *et al.*, *loc. cit.*, pp. 284, 286) is 2-*chloropropyl thiolbenzoate*.

Alderman, Brubaker, and Hanford (U.S.P. 2,212,141) showed that ethylene sulphide reacts with acetic anhydride in the presence of a small quantity of pyridine to give the diacetate of 2-mercaptoethanol. They give, however, no details of the reaction with an asymmetrical sulphide, and it is now found that the main product (over 58% yield) from propylene sulphide is 2-*acetylthiopropyl acetate* (X). Possibly some (III) is also formed, although there is no evidence of its presence. The structure of (X) is proved by converting it into the corresponding 2-*mercaptopropan*-1-*ol* (XI), the boiling point of which is higher than that of the isomeric (IV). The 2 : 4-*dinitrophenyl thioether* [XIII; R = 2 : 4-$(NO_2)_2C_6H_3$] derived from (XI) has a much lower melting point than the isomer (VI). Though (XIII) is a primary alcohol, no carboxylic acid was isolated on oxidation with chromic acid, and potassium permanganate gives potassium 2 : 4-dinitrobenzene sulphonate. This permanganate oxidation, perhaps caused by the sulphur atom in (XIII) being attached to a secondary carbon atom, is again different from that of 2-(2 : 4-dinitrophenylthio)ethan-1-ol, which gives the disulphone. Further, (XI) reacts with two moles of phenyl *iso*cyanate to form a *derivative* (XIV) different from (V). Hence, the structure of (XI) and the normal ring-opening of propylene sulphide by acetic anhydride in the presence of pyridine are definitely established.

Apparently, aqueous hydrochloric acid, like acetyl chloride and bromide, reacts abnormally with propylene sulphide, as a 50% yield of a liquid regarded as 2-chloropropane-1-thiol (IX) is isolated, and this is identical with the product obtained by hydrolysis of 2-chloropropyl thiolacetate (II). It is possible that the fission of propylene sulphide with hydrochloric acid leads to some of the normal isomer which then may give rise to some of the higher-boiling material obtained, just as the necessarily normal opening of ethylene sulphide with hydrochloric acid (Delépine and Eschenbrenner, *Bull. Soc. chim.*, 1923, **33**, 703) also yielded a high-boiling fraction. Samples of (IX), prepared by the four methods indicated in the diagram, seem to be identical, since there is no significant difference in their refractive index or boiling point, and they give identical *thiolurethanes* (XVII) with phenyl and α-naphthyl *iso*cyanate. On attempting

to prepare the 2 : 4-dinitrophenyl thioether from (IX), the alkaline conditions required for the reaction result in the conversion of (IX) into propylene sulphide or a polymer (cf. the preparation of ethylene sulphides from 1 : 2-chloro-thiols, Coltof, U.S.P. 2,783,860), and no derivative is formed. However, (IX) obtained from (IV) or (XI) by hydrochloric acid, reacts with picryl chloride in the presence of sodium acetate to form the crystalline *thioether* (XVIII), which is also obtained from (VI) by phosphorus pentachloride. Because of the mild alkaline conditions employed, this production of (XVIII) from different samples of (IX) constitutes the best proof of their identity.



R = 2 : 4-$(NO_2)_2C_6H_3$– or 2 : 4 : 6-$(NO_2)_3C_6H_2$–.
hydr. = hydrolysis by 1% methanolic hydrogen chloride.

The compound regarded as 2-chloropropane-1-thiol (IX) was first prepared by Sjöberg (*loc. cit.*) by the interaction of 1-mercaptopropan-2-ol (IV) and aqueous hydrochloric acid. However, this is no proof of structure, as the same compound is found to be similarly obtained from the isomeric 2-mercaptopropan-1-ol (XI). Apart from the fact that (IX) is obtained on hydrolysis of 2-chloropropyl 1-thiolacetate (II), the formula assigned to it is thought probable for the following reasons. Bennett and Hock (*J.*, 1925, **127**, 2671; Bennett, *Trans. Faraday Soc.*, 1941, **37**, 796) were the first to explain a number of fissions of carbon–sulphur links by means of an intermediary sulphonium ion. Ions of the type (XII) would be expected to be unstable, as it has been shown by Culvenor *et al.* (*loc. cit.*, p. 284) that the ring in aliphatic ethylene sulphides undergoes fission when the higher valency of sulphur is invoked. The rupture of (XII) to form a carbonium ion would, by analogy with the numerous nucleophilic attacks on the $C_{(2)}$ of propylene, be expected to produce (IX) rather than the unknown isomeric chloropropanethiol. This sulphonium ion concept explains the similar conversion (Fuson, Price, and Burness, *J. Org. Chem.*, 1946, **11**, 477), by hydrochloric acid, of both R·S·CHMe·CH_2·OH and R·S·CH_2·CHMe·OH into R·S·CH_2·CHMeCl (where R = Et). A similar rearrangement involving nitrogen instead of sulphur is described by Schultz and Sprague (*J. Amer. Chem. Soc.*, 1948, **70**, 48).

The base-catalysed alcoholysis of propylene oxide (Chitwood and Freure, *loc. cit.*) is analogous to the normal opening of propylene sulphide with acetic anhydride containing pyridine, and can be attributed to the presence of pyridine acetate and to the acetate ion reacting with $C_{(1)}$ which has a lower electron density than $C_{(2)}$. The thiol group formed is then acetylated. It is noteworthy that this normal reaction is very much slower than the abnormal one with acetyl chloride.

The abnormal opening of the propylene sulphide ring by acetyl chloride and bromide, and

probably by hydrochloric acid, affords interesting implications when compared with the action of such reagents on ethylene oxides. Propylene oxide and hydrochloric acid give the normal product almost entirely (Smith, *Z. physikal. Chem.*, 1919, **93**, 59), though acid-catalysed alcoholysis yields a mixture of normal and abnormal products (Chitwood and Freure, *loc. cit.*). There appears not to be a record of the action of acetyl halides on propylene oxide, but Sjöberg (*Chem. Abstr.*, 1943, **37**, 4363) shows that the product (73% yield) of the interaction of acetyl chloride and epichlorohydrin is normal, and that the product (37% yield) from glycidol is 92% normal. Similar results are obtained in the reaction of glycidol and epichlorohydrin with allyl alcohol in the presence of acid (Swern, Billen, and Knight, *J. Amer. Chem. Soc.*, 1949, **71**, 1152). The sulphur in ethylene sulphides is known to exert its higher valency towards methyl iodide far more easily than does the oxygen in ethylene oxides (Culvenor *et al.*, *loc. cit.*, p. 285) and it is tentatively suggested that hydrochloric acid and acetyl halides likewise form an onium ion to a greater extent with ethylene sulphides than with oxides. This would account for formation of much larger amounts of abnormal products from ethylene sulphides than from ethylene oxides.

Further work on a comparison of reactions of ethylene oxides and sulphides is being carried out. It is already clear that a deduction of the reactions of ethylene sulphides from formal analogy with those of ethylene oxides can be most misleading.

Experimental.

Reaction of Propylene Sulphide with Acetyl Halides.—Propylene sulphide was prepared from propylene oxide and thiourea by a modification of the method described by Culvenor, Davies, and Pausacker (*J.*, 1946, 1050). The preliminary stirring at 0° was omitted, the propylene sulphide added in portions, and the temperature maintained at 20° by efficient stirring and external temperature control during the whole reaction period of 3½ hours. Distillation of the product was effected without undue delay, fractionation giving a product, b. p. 74·5° (yield, 70%).

2-Chloropropyl thiolacetate (II) was prepared from propylene sulphide and acetyl chloride (Culvenor, Davies, and Heath, *J.*, 1949, 286). During fractionation, the b. p. (70—71°/9 mm.) and n_D^{25} (1·491) of the distillate remained constant. (II) was unchanged when boiled with dry pyridine in benzene, but was converted into high-boiling material by interaction with sodium cyanide in alcohol in the presence of a phenol buffer.

(II) (7·6 g.), anhydrous potassium acetate (7 g.), glacial acetic acid (5 ml.), and acetic anhydride (1 ml.) were refluxed until precipitation of potassium chloride ceased (3 hours). The cold mixture was agitated for a short time with water (30 ml.). The washed and dried ethereal extract gave 1-*acetylthio*-2-*propyl acetate* (III) (3·5 g.), b. p. 119—121°/19 mm., having a slight, pleasant odour (Found: C, 47·45; H, 7·05. $C_7H_{12}O_2S$ requires C, 47·7; H, 6·8%). The b. p. and n_D^{25} (1·467) were constant throughout the distillation.

1-Mercaptopropan-2-ol (IV) was obtained when (III) (3 g.) was heated under reflux with 1% methanolic hydrogen chloride (7 ml.) for 6 hours, the mixture being then distilled. (IV), b. p. 70—71°/20 mm., n_D^{25} 1·4815, is completely miscible with water, has an odour resembling that of mercaptoethanol, and gives colour tests characteristic of primary and secondary mercaptans (violet with aqueous sodium nitroprusside, and red with nascent nitrous acid). Sjöberg (*loc. cit.*) recorded b. p. 51°/12 mm. and n_D^{25} 1·4862 for the compound which he assumed to be 1-mercaptopropan-2-ol. (IV) and 2 moles of phenyl *iso*cyanate (cf. Bennett, *J.*, 1922, **121**, 2145) at 100° (2 hours) gave *propylene 2-phenylcarbamate 1-phenylthiolcarbamate* (V), m. p. 140·5°, prisms from alcohol–light petroleum (Found: N, 8·9. $C_{17}H_{18}O_2N_2S$ requires N, 8·5%). (IV) (0·1 g.) and picryl chloride (0·25 g.) were dissolved in alcohol (10 ml.), and a solution of anhydrous sodium acetate (0·1 g.) in alcohol (5 ml.) was added gradually with thorough mixing, a red colour being produced. After 5 minutes the mixture was warmed on the water-bath for 10 minutes. Addition of water gave 1-*picrylthiopropan*-2-*ol* (VI), m. p. 68°, lustrous light-yellow plates from aqueous alcohol (Found: N, 13·65. $C_9H_9O_7N_3S$ requires N, 13·85%). 1-(2 : 4-*Dinitrophenylthio*)*propan*-2-*ol* [VI; R = 2 : 4-$(NO_2)_2C_6H_3$], m. p. 94°, yellow warts from benzene–light petroleum (Found: N, 11·0. $C_9H_{10}O_5N_4S$ requires N, 10·85%), was obtained from equimolar proportions of (IV), 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol (cf. Bennett and Whincop, *J.*, 1921, **119**, 1863). As shown by a mixed m. p., (VI) was also obtained from 1-bromopropan-2-ol, 2 : 4-dinitrothiophenol, and sodium hydroxide in alcohol, the reactants being warmed on the water-bath for 1 hour (cf. Willgerodt, *Ber.*, 1885, **18**, 328).

(2 : 4-*Dinitrophenylthio*)*acetone* [VII; R = 2 : 4-$(NO_2)_2C_6H_3$], m. p. 139°, pale yellow needles from aqueous dioxan (Found: N, 11·2; S, 12·85. $C_9H_8O_5N_4S$ requires N, 10·95; S, 12·5%), was obtained (*a*) when (VI) (0·5 g.) was dissolved in the minimum volume of glacial acetic acid, and a solution of sodium dichromate (0·7 g.) in dilute sulphuric acid (5 ml.) added gradually, the mixture being then boiled for 5 minutes, and (*b*) on warming equimolar quantities of bromoacetone, 2 : 4-dinitrothiophenol, and sodium hydroxide in alcohol for 10 minutes, as evinced by a mixed m. p. determination. (VII) is sparingly soluble in alcohol and its dioxan solution gives a red precipitate on treatment with a warm solution of *p*-nitrophenylhydrazine hydrochloride and does not decolourise cold dilute permanganate.

1-Mercaptopropan-2-ol (IV), prepared according to the method of Sjöberg (*loc. cit.*), had properties similar to those of a sample prepared by hydrolysis of (III) (*e.g.*, n_D^{25} 1·484, b. p. 50—55°/10 mm.). It reacted with 1-chloro-2 : 4-dinitrobenzene to give (VI), as evinced by a mixed m. p. determination.

2-Bromopropyl thiolacetate was obtained in 95% yield when propylene sulphide (14·8 g.) was added in small portions with slight agitation and external cooling to freshly distilled acetyl bromide (15·3 ml.), and the mixture was kept at 35° for 2½ hours before distillation (Found: S, 15·65. C_5H_9OSBr requires S, 16·25%). This liquid, b. p. 45°/0·2 mm. (85—88°/10 mm. with slight decomposition), n_D^{25} 1·521, if

freshly distilled has the pleasant odour characteristic of thiol esters. However rapid decomposition occurs in air with development of the highly unpleasant odour of a halogeno-thiol and formation of hydrogen bromide. 2-Bromopropyl thiolacetate is stable in contact with aqueous sodium hydrogen carbonate. The pure liquid may be stored without decomposition in a sealed ampoule. Reduction of the ester with zinc dust and glacial acetic acid at 100° gave a halogen-free oil with an unpleasant odour, b. p. 96—104°/15 mm., n_D^{15} 1·458, which was apparently not the desired propyl thiolacetate as it is unchanged on attempted hydrolysis. Reduction of the ester with tin and hydrochloric acid caused rapid hydrolysis and subsequent polymerisation. Treatment with sodium acetate, using the method as described for the chloro-ester and potassium acetate, also yielded 1-acetylthio-2-propyl acetate (III), b. p. 112—114°/15 mm. (55% yield, the balance being polymer); its identity was established by hydrolysis with 1% methanolic hydrogen chloride to give 1-mercaptopropan-2-ol (IV), b. p. 58—60°/15 mm., identified by a mixed melting point determination of its 2 : 4-dinitrophenyl thioether (VI) which was obtained in 80% yield.

Reaction of Propylene Sulphide with Acetic Anhydride.—Propylene sulphide (14·6 g.), freshly distilled acetic anhydride (25 g.), and pyridine (1·5 ml.) were heated under reflux on the water-bath for 6 hours and then in an oil-bath at 130° for a further 3 hours. The product distilled over the range 97—103°/10 mm., further fractionation yielding *2-acetylthiopropyl acetate* (X), b. p. 103—105°/11 mm., n_D^{15} 1·4702 (20·6 g.) (Found: C, 47·5; H, 7·0. $C_7H_{12}O_3S$ requires C, 47·7; H, 6·8%). It has a slight, pleasant odour. Hydrolysis [method as for isomer (III)] yielded *2-mercaptopropan-1-ol* (XI), b. p. 60—62°/12 mm., 68°/25 mm., n_D^{15} 1·4818 (Found: C, 37·85; H, 8·6. C_3H_8OS requires C, 39·1; H, 8·7%). Like its isomer (IV), it is completely miscible with water, has a slightly unpleasant odour, and gives a mauve colour with sodium nitroprusside and a red colour with nitrous acid. During distillation of (X) and (XI) no change occurred. On heating (XI) at 100° for 2 hours with two moles of phenyl *iso*cyanate *propylene 1-phenylcarbamate 2-phenylthiolcarbamate* (XIV), m. p. 157·5°, prisms from aqueous alcohol (Found: N, 8·7. $C_{17}H_{18}O_2N_2S$ requires N, 8·5%), were obtained.

2-(2 : 4-Dinitrophenylthio)propan-1-ol [XIII; R = 2 : 4-$(NO_2)_2C_6H_3$], m. p. 64°, yellow warts from benzene–light petroleum (Found: C, 41·8; H, 3·7. $C_9H_{10}O_5N_2S$ requires C, 41·85; H, 3·85%), was obtained from (XI), 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol [method as for (VI), crystallisation being difficult]. Oxidation of (XIII) with chromic acid gave a polymer and water-soluble material which is difficult to extract. Oxidation at 70° with 3% aqueous potassium permanganate gave potassium 2 : 4-dinitrobenzenesulphonate (Found: N, 10·15. Calc. for $C_6H_3O_7N_2SK$: N, 9·8%), which explodes on heating and is soluble in water. 1-(2 : 4-Dinitrophenylthio)propan-2-ol, prepared by the method of Bennett and Whincop (*loc. cit.*) from mercaptoethanol, 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol, when similarly oxidised with potassium permanganate yielded white plates, m. p. 183—185°, on extraction with ether. The m. p. was not depressed on admixture with an authentic specimen of 2 : 4-dinitrophenylsulphonylmethane.

Reaction of Propylene Sulphide with Hydrochloric Acid.— A solution of propylene sulphide (14·8 g.) in methanol (20 ml.) was added with shaking and external cooling to a solution of concentrated aqueous hydrochloric acid (25 ml.) in methanol (30 ml.), and the mixture set aside for 19 hours, after which an unpleasant-smelling oil separated. Water (100 ml.) was added and the oil extracted with chloroform without delay, washed, dried ($CaCl_2$), and distilled. A small amount of propylene sulphide distilled and then a fraction, b. p. 59—61°/80 mm. Redistillation gave 2-chloropropane-1-thiol (IX), b. p. 124—125°/760 mm., 60°/80 mm.; n_D^{15} (1·484) of the distillate did not vary during the distillations, even when a fractionating column was used. The yield was 11·0 g., higher-boiling halogen-containing liquids comprising the balance. Sjöberg (*loc. cit.*) records b. p. 125—125·5°/764 mm., n_D^{20} 1·4852 for the compound which he assumes to be 2-chloropropane-1-thiol, and reports it to be decomposed immediately by aqueous alkali. Though (IX) does not form a derivative with 1-chloro-2 : 4-dinitrobenzene and sodium hydroxide, or with 1-fluoro-2 : 4-dinitrobenzene and sodium acetate, the unpleasant odour of the halogeno-thiol is replaced by the rather fragrant odour of propylene sulphide, and sodium chloride is precipitated. (IX) is comparatively inert to phenyl *iso*cyanate, heating in a sealed tube at 160° for 3 hours being necessary to effect conversion into *2-chloropropyl 1-phenylcarbamate* (XVII), m. p. 91·5°, prisms from light petroleum containing a few drops of benzene (Found: N, 6·3; S, 14·35. $C_{10}H_{12}ONSCl$ requires N, 6·1; S, 13·95%); this derivative is obtained in good yield from both first and last fractions of the distillate. Similarly (IX) reacts with α-naphthyl *iso*cyanate to give *2-chloropropyl 1-α-naphthylthiolcarbamate*, m. p. 110° (Found: N, 5·0. $C_{14}H_{14}ONSCl$ requires N, 5·0%). 2-Chloropropane-1-thiol (IX) was again obtained when 2-chloropropyl thiolacetate (II) (7·6 g.) was heated under reflux for 2 hours with 2% methanolic hydrogen chloride. Distillation gave 3·4 g. of product, b. p. 67—68°/85 mm., 124—125°/760 mm., n_D^{15} 1·484, which yielded with phenyl and α-naphthyl *iso*cyanates, respectively, the derivatives reported above. The residue from the distillation was a mobile, halogen-containing liquid of very high b. p. Distillation of a crude sample of (IX) at atmospheric pressure resulted in profound decomposition and the product contained hydrogen chloride and a liquid (b. p. 77°) with the odour of propylene sulphide; this, on storage, was replaced by that of the chloro-thiol.

2-Chloropropane-1-thiol (IX), prepared according to Sjöberg (*loc. cit.*) by treatment of 1-mercaptopropan-2-ol (IV) with concentrated aqueous hydrochloric acid, had b. p. 58—60°/80 mm., 124—125°/760 mm., n_D^{15} 1·486, and n_D^{15} 1·487. The yield was 66%, the residue consisting of high-boiling halogen-containing liquid. (IX) prepared by this method also gives derivatives with phenyl and α-naphthyl *iso*cyanates identical with those from (IX) prepared from propylene sulphide and hydrogen chloride. Also, (IX) (0·15 g.), picryl chloride (0·24 g.), and anhydrous sodium acetate (0·2 g.) in alcohol (5 ml.), on storage for 16 hours and dilution with water, yielded *2-chloro-1-picrylthiopropane* (XVIII; R = picryl), m. p. 88°, small yellow needles from benzene–light petroleum (Found: N, 12·85. $C_9H_9O_6N_3SCl$ requires N, 13·05%). (XVIII), which contained halogen, gave an appreciable depression in m. p. on admixture with picryl chloride, but not with the product obtained on treatment of (VI) in chloroform with phosphorus pentachloride, followed by evaporation of the solvent and pouring of the mixture into water.

2-Mercaptopropan-1-ol (XI) (4·2 g.) and concentrated aqueous hydrochloric acid (17 ml.) were warmed

on the water-bath. An immediate turbidity developed, and after 15 minutes the mixture was cooled and the oily layer extracted with ether, dried ($CaCl_2$), and distilled. The distillate, b. p. 41°/30 mm., 55°/50 mm., 62°/70 mm., n_D^{25} 1·488, gave steady boiling points when distilled at different pressures. With phenyl isocyanate and picryl chloride respectively it gave derivatives identical with those obtained from (IX) prepared by the interaction of (IV) and hydrogen chloride.

The micro-analyses were made by N. L. Lottkowitz and N. W. Gamble. One of us (W. E. S.) acknowledges financial assistance from the Commonwealth Reconstruction Training Scheme.

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70. *Experiments on the Synthesis of Carbonyl Compounds. Part I. Introduction. The Acidolysis of Acylmalonic Esters.*

By R. E. BOWMAN.

The initial aims of the present series of papers are outlined. Acid-catalysed acidolysis of acylmalonic esters (IV) is shown to furnish the methyl ketones (VI) in high yield. Conditions have been found for the isolation of the intermediate β-keto-esters (V) in moderate yields.

DESPITE comparatively recent developments such as the use of cadmium dialkyls (Cason, *Chem. Reviews*, 1947, **40**, 15) and the general β-keto-ester synthesis devised by Breslow, Baumgarten, and Hauser (*J. Amer. Chem. Soc.*, 1944, **66**, 1286) a number of the more complex polyfunctional types of carbonyl compounds remain inaccessible. Whilst there can be little doubt that the method employing organo-cadmium compounds is convenient for preparing the simpler types of ketones, its general application is inevitably limited by the usual restrictions accompanying the use of Grignard reagents; on the other hand, methods involving the use of β-keto-esters are frequently unsatisfactory owing to low yields at one or more of the many stages involved, *viz.*, the synthesis of the β-keto-esters, mono- or di-alkylation, and eventual ketonic hydrolysis, sometimes under severe conditions (Renfrow, *J. Amer. Chem. Soc.*, 1944, **66**, 144).

Examination of the problem of developing a more general method suggested that a promising route lay in the simple metathetical reaction between acid chlorides and sodiomalonic esters, provided that the degradation of the β-keto-diester (I) could be realised.

$$R{\cdot}COCl + R'{\cdot}CNa(CO_2Et)_2 \longrightarrow \underset{(I.)}{R{\cdot}CO{\cdot}CR'(CO_2Et)_2} \longrightarrow R{\cdot}CO{\cdot}CH_2R'$$

Compounds (I) have been prepared on various occasions during the last fifty years but have rarely been used in synthetical operations owing to the ease with which they suffer disruption into their original components (except where R′ = H) under the action of the normal hydrolytic reagents (Michael, *Amer. Chem. J.*, 1892, **14**, 510; Robinson and Robinson, *J.*, 1925, **127**, 175). The problem, therefore, resolved itself into that of finding conditions for generating the free acylmalonic acids from their esters whilst leaving intact the rest of the molecule, spontaneous or subsequent thermal decarboxylation of the keto-acid (II) to the ketone (III) being expected to occur quantitatively.

$$(I) \longrightarrow \underset{(II.)}{R{\cdot}CO{\cdot}CR'(CO_2H)_2} \longrightarrow \underset{(III.)}{R{\cdot}CO{\cdot}CH_2R'} + 2CO_2$$

This and the subsequent paper report two different approaches to this problem, and in both cases new methods of ketone synthesis have been elaborated. Experiments on the removal of one carbethoxy-group from acylmalonic and the analogous acylcyanoacetic esters, with the object of obtaining β-keto-esters and β-keto-nitriles respectively, will be reported later.

Acidolysis of Acylmalonic Esters.—Acylmalonic esters (IV) are, in general, high-boiling, viscous liquids or low-melting solids existing mainly in the enolic form and hence readily soluble in aqueous alkalis, in which media they are readily hydrolysed to their progenitors (Michael, *loc. cit.*). Therefore, use of alkaline conditions to bring about ketonic hydrolysis offers little hope of success. In recent years, however, the required degradation has been realised by several groups of workers (Giacolone, *Gazzetta*, 1936, **65**, 1127; Adickes, *J. pr. Chem.*, 1943, **161**, 271; Fuller, Tonkin, and J. Walker, *J.*, 1945, 633; H. G. Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386) employing strong acids. The technique developed by Walker and Hauser, whereby the crude acylmalonic esters prepared from the acid chloride and ethoxymagnesiomalonic ester (Lund, *Ber.*, 1934, **67**, *B*, 935) are subjected to boiling aqueous sulphuric acid in acetic acid

solution, has been shown to be extremely useful for the preparation of ketones R·CO·CH_2 where R is aromatic; the reaction failed completely when R was a straight-chain alkyl group such as n-amyl and for the fully substituted compounds (I; R = NO_2·C_6H_4, R′ = Bu^t).

It seemed possible that a more general solution to this problem might be realised by the use of acid-catalysed acidolysis according to the following scheme:

$$\text{(IV.)}\quad \text{R·CO·CH(CO}_2\text{Et)}_2 \xrightleftharpoons[\text{R′·CO}_2\text{H}]{\text{H}^+} \text{R′·CO}_2\text{Et} + \text{R·CO·CH(CO}_2\text{H)·CO}_2\text{Et} \xrightarrow{-\text{CO}_2} \text{R·CO·CH}_2\text{·CO}_2\text{Et}\quad \text{(V.)}$$

$$\text{(VI.)}\quad \text{R·CO·CH}_3 \xleftarrow{-\text{CO}_2} \text{R·CO·CH}_2\text{·CO}_2\text{H} + \text{R′·CO}_2\text{Et} \qquad \Big\Uparrow \text{H}^+;\ \text{R·CO}_2\text{H}$$

The initial experiments were carried out by refluxing a mixture of benzoylmalonic ester (1 mol.) and acetic acid (8 mols.) containing 1% sulphuric acid as catalyst. The expected reaction was found to occur with evolution of carbon dioxide and formation of acetophenone, benzoylacetic ester, and some unchanged starting material. Although the isolation of some β-keto-ester was highly satisfactory, attention at this stage of the work was focussed on the problem of forcing the reaction to completion. Substitution of propionic acid for acetic acid led to a considerable improvement in the yield of ketone although a small quantity of β-keto-ester still remained. Finally the technique of refluxing the acylmalonic ester (1 mol.) with propionic acid (5—8 mols.) and sulphuric acid (1% by weight of reactants) for 3 hours, followed by a short treatment with 10% sulphuric acid to complete the hydrolysis of any residual β-keto-ester, was adopted. In this manner benzoylmalonic ester yielded acetophenone in practically quantitative yield.

Nevertheless, the isolation of the acylmalonic esters was both wasteful of materials and restrictive in scope in view of the high boiling points of even the lower members of the series and hence conditions were sought for obtaining the highest possible yield of crude acylmalonic esters. The technique employed by Walker and Hauser (*loc. cit.*) suffers from the disadvantage that the reaction is carried out in the presence of free ethanol employed in the formation of the magnesium derivative. It seemed that the presence of the latter, together with that inevitably formed in the reaction, would considerably lower the yield of keto-ester, particularly in the aliphatic series. The preparation of ethoxymagnesiomalonic ester was therefore effected in benzene solution, using only a slight excess of ethanol which was finally removed as its azeotrope with benzene; in this manner ethanol-free solutions of the magnesium complex were readily obtained. Treatment of this reagent (100% excess) with the requisite acid chloride, followed by recovery of excess of malonic ester by distillation, yielded the crude keto-diester which on acidolysis as above furnished the methyl ketone R·CO·CH_3 in very high yield.

In this manner the acid chlorides of octanoic, undecanoic, dodecanoic, stearic, sebacic, *o*-chlorobenzoic, and *p*-nitrobenzoic acids, and of methyl hydrogen sebacate gave the corresponding methyl ketones. Even in the aromatic series, as shown by the last two examples, the yields by this process are considerably higher than those obtained by Walker and Hauser (*loc. cit.*).

Preparation of β-keto-esters from the corresponding acylmalonic esters was first described by Bernhard (*Annalen*, 1894, **282**, 166) who obtained benzoylacetic ester by steam-distillation of benzoylmalonic ester. Breslow *et al.* (*loc. cit.*) obtained propionylacetic ester similarly but in very poor yield. Recently, two new methods have been elaborated; first, the general β-keto-ester synthesis of Breslow *et al.* (*ibid.*) using the rather inaccessible ethyl *tert.*-butylmalonate, and, secondly, thermal pyrolysis of acylmalonic esters in the presence of toluene- or naphthalene-sulphonic acid (Riegel and Lilienfeld, *J. Amer. Chem. Soc.*, 1945, **67**, 1274).

The isolation of some of the intermediate β-keto-ester in the early experiments on the acidolysis of benzoylmalonic ester raised hopes that it might be possible to find conditions for obtaining the analogous aliphatic keto-esters. For this purpose a large quantity of lauroylmalonic ester was prepared and submitted in portions to the action of acetic acid (1 : 5) with various quantities of catalyst for various times. Limitation of time prevented a full examination of the reaction but under the best conditions found (3 hours at the boiling point using 0·22% sulphuric acid), a 48% yield of lauroylacetic ester (V; R = $C_{11}H_{23}$) and a 41% yield of the ketone (VI; R = $C_{11}H_{23}$) were obtained. A similar reaction applied to undec-10-enoyl chloride furnished *ethyl* 3-*ketotridec*-12-*enoate* * (V; R = CH_2:CH·$[CH_2]_8$) (45%) and the ketone (VI; R = CH_2:CH·$[CH_2]_8$) (41%). The reaction was finally investigated on a larger scale (1·25 mols.) using octanoyl chloride, ethyl 3-ketodecanoate (V; R = C_7H_{15}) (43%) together with methyl heptyl ketone (VI; R = C_7H_{15}) (52%) being obtained.

* Geneva nomenclature is used throughout this paper.

Finally the acidolysis of fully substituted acylmalonic esters (I; R = R′ = alkyl) was investigated, but in no case could the desired reaction be brought about. The failure of Renfrow (*loc. cit.*) to bring about a similar reaction with fully substituted β-keto-esters, CH_3·CO·CRR′·CO_2Et, may be significant in this connexion. In the course of this work *ethyl n-butyl isohexoylmalonate* (*6-keto-9-methyldecane-5 : 5-dicarboxylate*) (I; R = $(CH_3)_2$CH·CH_2·CH_2, R′ = Bu^n) was prepared.

Experimental.

Ethoxymagnesiomalonic Ester.—Magnesium (36 g., 1·5 mols.) was covered with dry benzene (110 ml.) containing absolute ethanol (10 ml.) in a three-necked flask fitted with a tap funnel and reflux condenser. After the addition of a crystal of iodine and/or carbon tetrachloride (1 ml.) a small portion of a solution (*A*) of ethyl malonate (commercial, undistilled; 240 g., 1·5 mols.), absolute ethanol (70 g., *i.e.*, 78 g. in all; 1·7 mols.) in dry benzene (300 ml.) was added and the mixture heated, if necessary, until a vigorous reaction set in. Solution (*A*) was then added at a convenient rate (2—3 hours) and the product refluxed until dissolution of the magnesium was complete. At this stage the reflux condenser was replaced by a fractioning column of the Widmer or Fenske type (30 cm. long) fitted with a reflux head, and the mixture was slowly distilled until most of the free ethanol had been removed as azeotrope with benzene (b. p. 68·4°) as shown by a tendency for the distillation temperature to rise to about 70°. The residue in the flask consisted of ethanol-free ethoxymagnesiomalonic ester in benzene solution (volume, approx. 700 ml.) and was ready for use.

Crude Acylmalonic Esters.—The requisite acid chloride (1 mol.) in dry benzene was added, with stirring and external cooling, to the benzene solution of ethoxymagnesiomalonic ester (2 mols.) during 30 minutes and the resulting mixture refluxed for 1 hour. The cooled solution was decomposed by addition to ice and dilute sulphuric acid, and the organic layer thoroughly shaken with more dilute sulphuric acid, followed by water (3 portions). Removal of the first portion of benzene from the dried solution (Na_2SO_4) was effected at room temperature under reduced pressure. The excess of malonic ester was then recovered by distillation at 0·5 mm. (bath-temperature up to 100°), in excellent yield. A fractionating column was not necessary at this stage when acids higher than heptanoic acid were used.

Complete Acidolysis.—A mixture of the crude acylmalonate (1 mol.), propionic acid (commercial; 6 mols.), and sulphuric acid (1% by weight of total weight of reactants) was boiled under reflux for 3 hours; a vigorous evolution of gas occurred in the early stages. Then sulphuric acid (75 ml. of 4*N*.) was added to the slightly cooled reaction mixture, and refluxing was continued until no further gas was evolved. The method of working up depended on the scale of the reaction and nature of the product.

Method A (*small scale*). The reaction product was poured into water, and the mixture neutralised by aqueous sodium hydroxide. The ketone, if solid, was then filtered off or, if liquid, taken up in a solvent and isolated in the usual manner. If the product was a keto-acid, it was extracted directly without neutralisation.

Method B (*small scale; non-volatile ketones*). The reaction mixture was poured into water, and steam passed into the mixture until the propionic acid was all removed. The product was then isolated from the residue as usual.

Method C (*large scale*). An excess (70% over that required for neutralisation of the sulphuric acid) of anhydrous sodium acetate was added to the acidolysis mixture which was then distilled under reduced pressure through a Vigreux column (20 cm. long) to remove ethyl propionate and most of the propionic acid. The residue was then worked up as described in method (A).

In this manner the following acid chlorides were converted into the respective methyl ketones.

Starting materials. Acid.	Acid chloride. B. p. or m. p.	Ketone, R·CO·CH_3. R.	Method.	B. p. or m. p.	Yield, %.
Octanoic	82°/15 mm.	*n*-Heptyl [1]	(C)	80°/10 mm.	93
Undecanoic	95°/15 mm.	*n*-Decyl [2]	(A)	107°/5 mm.	94
Lauric	136°/10 mm.	*n*-Undecyl [3]	(A)	27—28°	97
Stearic [4]	—	*n*-Heptadecyl [5]	(B)	55—56°	96
Sebacic	140°/1 mm.	*n*-9-Ketodecyl [6]	(A)	69°	93
Methyl hydrogen sebacate [7]	—	ω-Carboxyoctyl [8]	(B)	56°	100 [9]
o-Chlorobenzoic	90°/10 mm.	*o*-Chlorophenyl [10]	(A)	84°/3 mm.	98
p-Nitrobenzoic	72°	*p*-Nitrophenyl [10]	(B)	75—78°	90 [11]

[1] Semicarbazone, m. p. 117—118° (Dakin, *Amer. Chem. J.*, 1910, **44**, 48, reported m. p. 118°).
[2] Semicarbazone, m. p. 122—123° (Pickard and Kenyon, *J.*, 1911, **99**, 57, gave m. p. 122—123°).
[3] Semicarbazone, m. p. 117° (Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 685, and Asahina and Nakayama, *J. Pharm. Soc. Japan*, 1925, **52**, 65, gave m. p.s 115—116° and 118—119° respectively).
[4] Crude: prepared from the acid and thionyl chloride, with removal of the latter *in vacuo*. [5] Oxime, m. p. 77° (Thoms and Vogelsang, *Annalen*, 1907, **357**, 161, reported m. p. 77°). [6] Dodecane-2 : 11-dione, slender needles [from light petroleum (b. p. 40—60°)], m. p. 69° (Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 46, reported m. p. 67·4—67·8°) (Found: C, 72·4; H, 10·8. Calc. for $C_{12}H_{22}O_2$: C, 72·7; H, 11·1%). The *dioxime* crystallised from ethyl acetate and then benzene in prisms, m. p 114—115° (Found: N, 11·9. $C_{12}H_{24}O_2N_2$ requires N, 12·3%). [7] *Org. Synth.*, 1945, **25**, 71. [8] Crude. [9] Crystallised from benzene; m. p. 58° (Abraham, Mowat, and Smith, *J.*, 1937, 948, gave m. p. 59°); semicarbazone, m. p. 135° (*idem*, *ibid.*, m. p. 135—136°). [10] Semicarbazone, m. p. 159° (Wahl and Rolland, *Ann. Chim.*, 1928, [x], **10**, 29, reported m. p. 159—160°). [11] Crude. [12] Crystallised from benzene–light petroleum (b. p. 40—60°); m. p. 80° (Drewsen, *Annalen*, 1882, **212**, 160, gave m. p. 80—81°); oxime, m. p. 172° (Posner, *ibid.*, 1912, **389**, 43, gave m. p. 172—173°).

Partial Acidolysis. Preparation of β-Keto-esters.—The following conditions gave the best results: The crude acylmalonate (as above; 1 mol.), glacial acetic acid (5 mols.), and sulphuric acid (0·22% by weight of reactants) were boiled under reflux for 3 hours. Excess of barium carbonate (3 times the wt. of sulphuric acid) was then added to the cooled reactants, and the mixture set aside with occasional agitation for 1 hour. After filtration, the filtrate was carefully fractionated *in vacuo* in the presence of a trace of barium carbonate, through a Vigreux column.

Ethyl 3-Ketotetradecanoate.—In this manner lauroylmalonic ester (crude; 0·1 mol.) gave methyl undecyl ketone, b. p. 110—113°/5 mm. (9·7 g., 64%), and the keto-ester as a colourless oil, b. p. 128—130°/0·2 mm., n_D^{20} 1·4489 (13 g., 48%) (Found: C, 70·6; H, 10·8. Calc. for $C_{16}H_{30}O_3$: C, 71·1; H, 11·1%). The latter ester gave a deep-red ferric reaction and formed a *pyrazolone* which separated from methanol and then light petroleum (b. p. 40—60°) in colourless prisms, m. p. 67° (Found: N, 11·0. $C_{20}H_{36}ON_2$ requires N, 10·8%).

Ethyl 3-Ketodecanoate.—Crude octanoylmalonic ester (1·25 mols.) similarly furnished methyl heptyl ketone (93 g., 52%) and the keto-ester as a colourless oil, b. p. 84—86°/0·2 mm., n_D^{20} 1·4390, which gave a deep-red colour with aqueous-alcoholic ferric chloride (Found: C, 66·6; H, 10·0. Calc. for $C_{12}H_{22}O_3$: C, 67·3; H, 10·4%) (yield: 112 g., 43%). The pyrazolone separated from methanol and then light petroleum (b. p. 40—60°) in colourless prisms, m. p. 82° (Breusch and Keskin, *Rec. Fac. Sci. Univ. Istanbul*, 1946, **11**, *A*, 24, reported m. p. 82°) (Found: N, 9·0. Calc. for $C_{16}H_{28}ON_2$: N, 8·9%).

Ethyl 3-Ketotridec-12-enoate.—Undec-10-enoyl chloride (b. p. 98°/3 mm.; 41 g., 0·2 mol.) was treated with ethoxymagnesiomalonic ester (0·4 mol.), and the crude product partly acidolysed according to the general method. In this manner, dodec-11-en-2-one (15 g., 41%), b. p. 104°/5 mm. (semicarbazone, m. p. 122—123°), and *ethyl 3-ketotridec-12-enoate*, a colourless oil (23 g., 45%), b. p. 122—124°/0·4 mm., n_D^{20} 1·4485 (Found: C, 70·5; H, 10·6. $C_{15}H_{26}O_3$ requires C, 70·9; H, 10·2%), were obtained. The latter gave a deep-red ferric colour and formed a *copper* derivative which separated from ice-cold light petroleum (b. p. 40—60°) in pale green, slender needles, m. p. 75—77° [Found: Cu, 10·9. $Cu(C_{15}H_{25}O_3)_2$ requires Cu, 11·2%].

Ethyl 6-Keto-9-methyldecane-5 : 5-dicarboxylate.—Prepared in the usual manner (cf. Michael, *loc. cit.*) from isohexanoyl chloride and sodio-*n*-butylmalonic ester in ether, the *ester* was obtained as a colourless viscous oil, b. p. 120°/0·5 mm., n_D^{20} 1·4408 (Found: C, 64·9; H, 9·7. $C_{17}H_{30}O_5$ requires C, 65·0; H, 9·8%).

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71. *Experiments on the Synthesis of Carbonyl Compounds. Part II. A General Synthesis of Saturated Ketones*, R·CO·CH$_2$R'.

By R. E. BOWMAN.

The benzyl esters of acylmalonic acids (II) undergo hydrogenolysis with the formation of the parent keto-acids, which readily lose two molecules of carbon dioxide to give the corresponding ketones, R·CO·CH$_2$R'. The reaction appears to be of general application subject only to the absence of reducible substituents. A preliminary account of this work has already been published (*Nature*, 1948, **162**, 111).

IN the preceding paper a method of converting acylmalonic esters, R·CO·CH(CO$_2$Et)$_2$, into the ketones R·CO·CH$_3$ by acidolysis was described. Failure to extend this reaction to the fully substituted compounds R·CO·CR'(CO$_2$Et)$_2$ demonstrated the need of an entirely new approach to the problem. The hydrogenolytic fission of benzyl esters appeared to offer an alternative method of developing a general ketone synthesis as follows:

$$CH_2(CO_2{\cdot}CH_2Ph)_2 \longrightarrow R'{\cdot}CH(CO_2{\cdot}CH_2Ph)_2 \longrightarrow R'{\cdot}CNa(CO_2{\cdot}CH_2Ph)_2 \xrightarrow{R{\cdot}COCl}$$
(I.)

$$R{\cdot}CO{\cdot}CR'(CO_2{\cdot}CH_2Ph)_2 \xrightarrow{H_2\text{-}Pd} R{\cdot}CO{\cdot}CR'(CO_2H)_2 \longrightarrow R{\cdot}CO{\cdot}CH_2R' + 2CO_2$$

A critical examination of this route served to emphasise the difficulties likely to be encountered in the first stage of the synthesis owing, in particular, to the high boiling points (*e.g.*, benzyl malonate boils at *ca.* 170°/0·5 mm.) and low crystallising powers associated with benzyl esters in general: furthermore, there was also the possibility of some hydrogenolysis of the benzyl groups during the second stage of the process. Consideration of the possibilities involved, however, suggested that these difficulties might be avoided by forming the sodio-benzyl ester (I) *in situ* from the corresponding ethyl ester by ester interchange with benzyl alcohol in benzene solution, the sodium enol acting as catalyst for the interchange and the reaction being forced to completion by removal of the ethanol formed as its azeotrope with benzene. The next stages in the procedure would then consist of coupling of the sodio-derivative (I) with the requisite acid

chloride, catalytic debenzylation of the resulting keto-ester (II), and finally thermal decarboxylation of the acid (III) to the ketone (IV):

$$\text{(I)} + \text{R·COCl} \longrightarrow \underset{\text{(II.)}}{\text{R·CO·CR'(CO}_2\text{·CH}_2\text{Ph)}_2} \xrightarrow{4\text{H}} \underset{\text{(III.)}}{\text{R·CO·CR'(CO}_2\text{H)}_2} \longrightarrow \underset{\text{(IV.)}}{\text{R·CO·CH}_2\text{R'}}$$

This idea was first put to test using ethyl ethane-1 : 1 : 2-tricarboxylate (I; R′ = CH_2·CO_2Et) which was converted into its sodio-derivative in benzene in the usual manner and treated with benzyl alcohol (3 mols.). Ester interchange was found to proceed readily as shown by the elimination of ethanol which was obtained (as azeotrope with benzene) with the aid of a fractionating column in almost theoretical yield. The resulting tribenzyl sodio-ester (I; R′ = CH_2·CO_2·CH_2Ph) was then coupled with undecanoyl chloride, and the crude keto-ester (II; R = n-$C_{10}H_{21}$, R′ = CH_2·CO_2·CH_2Ph) submitted to catalytic debenzylation using palladised charcoal at atmospheric pressure and temperature in ethanolic solution. Considerable difficulties were encountered at this stage owing to catalyst poisoning, but eventually most of the required hydrogen was absorbed. Decarboxylation of the product proceeded smoothly at, or just below, the boiling point of the solvent (ethanol), the expected product, 4-ketotetradecanoic acid * (IV; R = $C_{10}H_{21}$, R′ = CH_2·CO_2H) being obtained in 66% yield.

At this stage of the work, attention was focussed on the purely practical aspects of the problem, namely, the purification of commercial benzyl alcohol and the finding of more effective catalysts. Initially, debenzylations were carried out in alcohol with palladised charcoal (iron-free) as catalyst; later mixtures of the latter and palladised strontium carbonate were used. More recently (unpublished results) the use of palladised strontium carbonate (10% of Pd) in ethyl acetate has been found to be most effective and is now the preferred procedure. As the result of these and subsequent experiments a general technique has been evolved and is described in full in the Experimental section.

By use of this technique, n-octanoyl chloride and n-octylmalonic ester yielded ***heptadecan-8-one*** (IV; R = C_7H_{15}, R′ = C_8H_{17}) (91%) which was characterised as the substituted ***hydantoin*** (Hense, *J. Amer. Chem. Soc.*, **1942**, **64**, 522), and similarly ***2-methylpentadecan-5-one*** [IV; R = $C_{10}H_{21}$, R′ = $(CH_3)_2CH{\cdot}CH_2{\cdot}CH_2$] (80%) was obtained as an oil which resisted our attempts at characterisation.

Sebacoyl chloride and n-octylmalonic ester (2 mols.) furnished ***octacosane-10 : 19-dione*** (V) in 78% yield, characterised as the ***dioxime*** and by reduction (Huang-Minlon, *J. Amer. Chem. Soc.*, **1946**, **68**, 2487) to the saturated paraffin, n-octacosane, together with the product of partial reaction, the known 10-ketononadecanoic acid (VI).

(V.) C_8H_{17}·CO·$(CH_2)_8$·CO·C_8H_{17} $\qquad$ C_8H_{17}·CO·$(CH_2)_8$·CO_2H (VI.)

(VIII.) C_8H_{17}·CHEt·CO·$(CH_2)_{11}$·CO_2H $\qquad$ OH·CHPh·CO·$C_{10}H_{21}$ (IX.)

The failure of the G. M. Robinson ketone synthesis (*J.*, **1930**, 745) when applied to the preparation of α-substituted ketones (*Ann. Reports*, **1939**, **36**, 300), and the low yields encountered in the use of the cadmium di-*sec.*-alkyls (Cason, *J. Amer. Chem. Soc.*, **1946**, **68**, 2078), made it of interest to determine whether any such steric factors would operate in the debenzylation reaction. Accordingly 2-ethylhexanoyl chloride was condensed with benzyl sodioundecane-1 : 1 : 11-tricarboxylate, and the product debenzylated and decarboxylated to yield ***13-keto-14-ethyloctadecanoic acid*** (VIII) in 78% yield (crude); this acid was purified through its ***ethyl*** ester and characterised as the ***p-phenylphenacyl ester***.

Attention was next turned to the synthesis of ketones containing groups other than alkyl or carboxy-groups. ω-Hydroxyundecanoic acid was converted by successive treatment with acetyl chloride and oxalyl chloride into the ω-acetoxy-acid chloride which, without isolation, was coupled with benzyl sodio-n-octylmalonate (I; R′ = C_8H_{17}) and furnished in the same manner ***11-ketoicosanol***, C_8H_{17}·CO·$(CH_2)_{10}$·OH, characterised as the ***oxime*** and by reduction (Clemmensen) to the known eicosanol. Acetylmandeloyl chloride and benzyl sodio-n-dodecylmalonate gave, by the general procedure, ***1-hydroxy-1-phenylpentadecan-2-one*** (IX) in 65% yield. (IX) was characterised by oxidation with chromic acid (cf. Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, **1947**, **30**, 1741) to the ***diketone*** and by reaction of the latter with o-phenylenediamine to give a ***quinoxaline***.

Finally, as an example in the aromatic series, m-anisoyl chloride and benzyl sodioethane-1 : 1 : 2-tricarboxylate were condensed, and the product debenzylated and decarboxylated to yield the known γ-keto-γ-m-methoxyphenylbutyric acid. The investigation is being continued.

* Geneva nomenclature is used throughout this paper.

Experimental.

Apparatus.—All-glass apparatus fitted with ground-glass joints lubricated with silicone grease was used. The fractionating column used in the ester interchanges contained a packed section (40 × 1·8 cm.) of single-turn glass helices (Fenske) and was fitted with a total condensation–partial take-off head of the Whitmore–Lux pattern.

Reagents.—Benzene. The benzene used in these experiments was commercial AnalaR benzene which had been stored over sodium wire.

Benzyl alcohol. Commercial "pure" benzyl alcohol was mixed with Raney nickel (5% w/w) and the mixture heated on the steam-bath for 3 hours with occasional agitation. After cooling, the alcohol was decanted from the bulk of the metal and distilled under reduced pressure. The distillate usually contained benzaldehyde which was separated by careful fractionation under reduced pressure in an atmosphere of nitrogen or by oximation followed by distillation.

Palladium–charcoal catalyst. The catalyst was prepared in the manner described in *Org. Synth.*, 1946, **26**, 78 (catalyst D), with two modifications. First, the iron was removed from the charcoal with 6*N*-hydrochloric acid and, secondly, hydrogen was thoroughly removed by evacuation from the reduction mixture *at the final stage* of preparation before air was admitted. This procedure allows drying of the catalyst at 120° without ignition.

Palladised strontium carbonate (ca. 10% of Pd). Palladous chloride (8·9 g.) was dissolved in AnalaR concentrated hydrochloric acid (21 ml.) at the b. p., and the solution, after dilution with water (400 ml.), added with vigorous stirring to a suspension of strontium carbonate ("precipitated"; 70 g.) in water (500 ml.) during 5 minutes. The temperature of the stirred mixture was then raised to 80° during 15 minutes, and the solid allowed to settle. The supernatant liquid was removed by syphoning and washing (5 l.) carried out in the same manner. The catalyst was then removed by filtration, dried at 120°, and finely powdered.

Acid chlorides. Unless otherwise specified, acid chlorides were prepared in the usual manner from the acid and thionyl chloride, except that a considerable amount of first runnings was rejected to avoid contamination with sulphur-containing substances.

General Methods.—Preparation of benzyl sodiomalonates. The requisite ethyl sodiomalonates were prepared by two methods. (*a*) The ethyl malonate in benzene solution was added in the usual manner to sodium which had been powdered under pure toluene or xylene, the solvent decanted, and the residue washed several times with AnalaR benzene. (*b*) Clean sodium (1 mol.) was dissolved in magnesium-dried ethanol (20 × wt. of sodium), and the solution distilled from a flask fitted with tap-funnel (guard-tube) and condenser leading to a Kon rectangle, in an oil-bath heated to 190°. When most of the ethanol had distilled off and a slight crust had formed on the surface of the residue, the pressure in the flask was rapidly lowered, resulting in the rapid removal of solvent and the production of a solid foam of sodium ethoxide. The oil-bath was then removed and the ethoxide allowed to cool *in vacuo*. The system was closed by means of the appropriate taps and the malonic ester (1 mol.) in benzene solution added from the tap-funnel. Formation of the sodium enol was immediate as shown by dissolution of the sodium ethoxide; air was then admitted through the guard-tube. Benzyl alcohol (1 mol. per carbalkoxy-group in the malonic ester) was added to the foregoing solution, and the mixture distilled through the fractionating column already described, under a reflux-ratio of about 5 : 1 so that the temperature did not rise above 69°/760 mm. The distillation of benzene–ethanol azeotrope was rapid at first but gradually slowed down towards the end of the interchange when distillation was carried out under a higher reflux-ratio (20 : 1) at about 1—3 drops per minute, the temperature gradually rising to *ca.* 79°. At this stage the interchange was considered complete, and the residue which consisted of a benzene solution of benzyl sodiomalonate was allowed to cool.

Method (*a*) was used in the preliminary experiments as it allowed the interchange to be followed quantitatively but later, when this was found to be substantially complete under the conditions employed, the second method was always used since, in practice, it was more convenient and furnished a cleaner product.

Benzyl acylmalonates. The acid chloride (0·98 mol.) in benzene solution was added to the benzene solution of the benzyl sodiomalonate (1 mol.), with stirring or shaking, during a few minutes, and the mixture refluxed for a further 30 minutes. The cooled reaction mixture was then added to ice-water containing a trace of sulphuric acid, and the organic layer separated. The aqueous layer was extracted with fresh benzene and the combined benzene extracts washed with water and dried (Na_2SO_4). Removal of solvent was carried out at room temperature under reduced pressure until all water had distilled off, and was finally completed at 100°/0·5 mm. The products were yellow or yellow-brown viscous oils.

Debenzylation and decarboxylation of benzyl acylmalonates. The foregoing product (0·5 mol.) was dissolved in absolute ethanol or a mixture of ethanol and ethyl acetate (solvent volume, *ca.* 200 ml.), and stirred in an atmosphere of hydrogen in the presence of palladised charcoal (10% of Pd; 4 g.) until absorption became slow owing to poisoning of the catalyst (frequently 1 l. taken up). At this stage the catalyst was either removed by filtration and fresh charcoal catalyst added, or palladised strontium carbonate (10% of Pd; 5 g.) was added to the hydrogenation mixture, and the hydrogenation continued. If the first procedure was adopted, it was sometimes necessary to repeat the process, rates of up to 200 ml. per minute being realised; with the second method somewhat slower rates (*e.g.*, 60 ml. per minute) of hydrogen absorption occurred. The temperature of the reaction mixture was kept below 30° by external cooling. Furthermore, it was found on occasions that the hydrogenation became slow owing to premature decarboxylation, and accordingly the flask was evacuated and refilled with fresh hydrogen before the addition of fresh catalyst. When the hydrogenation was complete, the catalyst was removed by filtration, and the filtrate raised to the b. p. under a reflux condenser, whereupon brisk evolution of carbon dioxide took place. On completion of this stage (30 minutes), the solvent was distilled off and the product isolated.

4-Ketotetradecanoic Acid.—Undecanoyl chloride (b. p. 93°/2 mm.; 25·1 g., 0·122 mol.) was treated

with the sodium enol of benzyl ethane-1 : 1 : 2-tricarboxylate (0·125 mol.) prepared from the ethyl ester (30·75 g., 0·125 mol.), sodium (2·9 g., 0·125 mol.) and benzyl alcohol (40·5 g., 0·375 mol.), and the product debenzylated and decarboxylated as described above. The product, after removal of solvent, was a semi-solid mass which was triturated with cold toluene (50 ml.). The solid (14 g.) was removed and the filtrate evaporated in an oil-bath at 170° to remove solvent and to decarboxylate any free ethanetricarboxylic acid. When cold, the residue was dissolved in ethyl acetate (100 ml.), and the solution washed with water and evaporated to dryness. Trituration of the residue with cold light petroleum (b. p. 40—60°) containing benzene (1%) furnished a further crop (6 g.). In this manner the total yield of crude keto-acid, m. p. 84—85°, was 20 g. (66%). The acid separated from benzene–light petroleum (b. p. 60—80°) in colourless plates, m. p. 87°; Robinson and Robinson (*J.*, 1926, 2206) give m. p. 87°. The oxime separated from light petroleum (b. p. 60—80°)–benzene (trace) in prisms, m. p. 74°, as described by the same authors.

Heptadecan-8-one.—The reactants were *n*-octoyl chloride (b. p. 81—82°/16 mm.; 19·9 g., 0·122 mol.) and benzyl sodio-*n*-octylmalonate (ethyl ester; 34 g., 0·125 mol.). The product was dissolved in light petroleum (b. p. 40—60°; 100 ml.) containing benzene (30 ml.), and the mixture treated with 2*N*-sodium hydroxide until alkaline. The organic layer was separated and the aqueous layer extracted again (2 × 50 ml. of same solvent mixture). The bulked extracts were washed with water and dried (Na_2SO_4), and the solvent removed by distillation, eventually, at 100°/0·2 mm. (to constant weight). The product readily solidified on cooling and was substantially pure *ketone* (26·2 g., 91%), m. p. 39—41°. It crystallised readily from methanol in colourless plates, m. p. 42° (Found: C, 80·4; H, 13·4. $C_{17}H_{34}O$ requires C, 80·3; H, 13·4%). The derived *hydantoin* (Henze, *loc. cit.*) separated from methanol in colourless tablets, m. p. 123° (Found: N, 8·3. $C_{18}H_{34}O_2N_2$ requires N, 8·6%).

2-Methylpentadecan-5-one.—The *ketone* was obtained in the same manner as in the previous experiment, from undecanoyl chloride (25·1 g., 0·122 mol.) and benzyl sodioisobutylmalonate, as a colourless oil, b. p. 134—136°/2 mm., m. p. 9—10°, n_D^{20} 1·4408 (23·4 g., 80%) (Found: C, 79·7; H, 13·2. $C_{16}H_{32}O$ requires C, 80·0; H, 13·3%). Attempts to prepare crystalline derivatives failed.

Octacosane-10 : 19-dione.—Sebacoyl chloride (b. p. 140°/1 mm.; 15 g., 0·062 mol.) was caused to react with benzyl sodio-*n*-octylmalonate (0·125 mol.) prepared as previously, and the product debenzylated and decarboxylated in the usual manner in ethanol–ethyl acetate solution (100 ml. : 50 ml.). The solution obtained after decarboxylation, furnished, on cooling, 15 g. of the ketone. Concentration of the filtrate to 25 ml. furnished a second crop (5·5 g.), the total yield of crude material, m. p. 92—94°, being 78%. *Octacosane-10 : 19-dione* separated from methanol as colourless plates, m. p. 95° (Found: C, 79·2; H, 12·6. $C_{28}H_{54}O_2$ requires C, 79·6; H, 12·8%). The *dioxime* crystallised from ethyl acetate in colourless prisms which melted at 68°, resolidified, and finally remelted at 78° (Found: N, 6·3. $C_{28}H_{56}O_2N_2$ requires N, 6·2%). A sample of the ketone was subjected to the modified Wolff–Kishner reduction (Huang-Minlon, *loc. cit.*), to give *n*-octacosane, colourless plates (from ethanol), m. p. 64° (lit., 64—65°).

The filtrate from the second crop of ketone was diluted with water (5 ml.) and neutralised hot with sodium hydroxide (4*N*.); on cooling, the sodium salt of the keto-acid separated (2·7 g.). The free acid, 10-ketononadecoic acid, obtained in the usual manner, crystallised from light petroleum (b. p. 80—100°) in colourless plates, m. p. 86—87°. Robinson and Robinson (*loc. cit.*) gave m. p. 86—87°. The oily oxime was treated with sulphuric acid to give the derived amide, m. p. 83°.

13-Keto-14-ethyloctadecanoic Acid.—A sample of 2-ethylhexanoic acid (Messrs. British Industrial Solvents, Ltd.) was converted into its acid chloride (b. p. 76°/20 mm.), and the latter (16·0 g., 0·098 mol.) treated with benzyl sodioundecane-1 : 1 : 11-tricarboxylate (0·1 mol.). The oily product obtained in the usual manner was refluxed with acetic acid (50 ml.) containing sulphuric acid (2 ml.; 20*N*.) for 30 minutes to decompose any keto-ester present. After dilution with water, the mixture was steam-distilled until free from steam-volatile materials, and the residual oil isolated with ether. The residue was extracted with light petroleum (b. p. 40—60°; 400 ml.) at 0°. Evaporation of the light petroleum extract furnished the crude keto-acid (25·5 g., 78%) which was substantially pure since it was solid at room temperature (22°). A sample (10 g.) was purified by conversion into its *ethyl* ester (by azeotropic esterification), which distilled as a colourless oil, b. p. 186—192°/0·2 mm., n_D^{20} 1·4480 (Found: C, 74·0; H, 11·6. $C_{22}H_{42}O_3$ requires C, 74·6; H, 11·9%).

The ester was hydrolysed with boiling aqueous-alcoholic sodium hydroxide (*N*.), and the free *keto-acid* isolated as a colourless oil, b. p. 203—204°/0·3 mm., m. p. 24—25·5° (thermometer in liquid; faintly cloudy melt), n_D^{20} 1·4580 (Found: C, 73·4; H, 11·7. $C_{20}H_{38}O_3$ requires C, 73·6; H, 11·7%). It formed a *p-phenylphenacyl* ester which separated from moist ethanol (norite) at 0° in interlocking colourless needles, m. p. 43° (Found: C, 78·2; H, 9·1. $C_{34}H_{50}O_4$ requires C, 78·6; H, 9·4%).

11-Ketoeicosanol.—11-Hydroxyundecanoic acid (24·8 g., 0·122 mol.) was dissolved in dry AnalaR benzene (50 ml.), and acetyl chloride (13 ml.) added during 10 minutes. The solution was then refluxed for a further 10 minutes, and the solvent and excess reagent were removed by distillation under reduced pressure. The residual acetoxy-acid was dissolved in fresh, dry AnalaR benzene (50 ml.), and oxalyl chloride (45 g., 0·35 mol.) added. After the vigorous reaction had subsided, the mixture was refluxed on the steam-bath for 0·5 hour, and solvent and unchanged chloride removed by distillation under reduced pressure, eventually at 90°/0·5 mm. The yield of crude acetoxyundecanoyl chloride was 33·0 g. (calc., 32·2 g.). The chloride in benzene solution was brought into reaction with benzyl sodio-*n*-octylmalonate (0·125 mol.), and the reaction product isolated as described for heptadecan-8-one. The product remaining after evaporation of the solvent was hydrolysed with boiling alcoholic potassium hydroxide (*N*.; 100% excess) and isolated by dilution with water. *11-Ketoeicosanol* was thus obtained as a white solid (22·9 g., 60%), m. p. 74—76°, which crystallised from ethanol and then light petroleum (b. p. 60—80°) in interlocking needles, m. p. 77° (Found: C, 76·8; H, 12·6. $C_{20}H_{40}O_2$ requires C, 76·9; H, 12·8%). It was characterised as the *oxime* which separated from benzene–light petroleum (b. p. 40—60°) at 0° in slender needles, m. p. 38—38·5° (Found: N, 4·4. $C_{20}H_{41}O_2N$ requires N, 4·3%), and by Clemmensen reduction in the usual manner to *n*-eicosanol, prisms (from methanol), m. p. 64—65° (Levene and Taylor, *J. Biol. Chem.*, 1924, **59**, 915, reported m. p. 65—65·5°).

1-Hydroxy-1-phenylpentadecan-2-one.—Acetylmandelyl chloride (34·8 g., 0·163 mol.) was condensed with benzyl sodio-α-dodecylmalonate (0·167 mol.) as before. The residue obtained after decarboxylation and removal of solvent was dissolved in light petroleum (b. p. 40—60°)–ethyl acetate (1 : 1), and the mixture made alkaline with aqueous sodium hydroxide. Considerable difficulty in separation of the phases owing to emulsification was encountered, but eventually the extraction was completed. The combined organic extracts (500 ml.) were washed with water, and the solvent was removed by distillation. The residue was gently warmed with aqueous alcoholic sodium hydroxide (N.; 0·16 mol.) for 15 minutes, and the product isolated by dilution with water. The crude *acyloin* (35 g., 65%), m. p. 50—53°, was slightly yellow, owing presumably to the presence of the corresponding diketone. It was crystallised several times from methanol and then light petroleum (b. p. 40—60°), whence it separated as tiny colourless prisms, m. p. 60° (Found: C, 78·8; H, 10·9. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·7%).

The acyloin (1·5 g.) in acetic acid (20 ml.) containing sulphuric acid (2 ml. of 20N.) was treated dropwise at room temperature with chromic acid (10N.) until the solution assumed a permanent orange-red colour. Dilution with water afforded the product as a yellow oil which readily solidified. Crystallisation from methanol at 0° and then from light petroleum (b. p. 40—60°) furnished the *diketone* as yellow plates, m. p. 52—53° (Found: C, 79·3; H, 10·4. $C_{21}H_{32}O_2$ requires C, 79·6; H, 10·2%). The diketone (1·58 g., 0·05 mol.) and *o*-phenylenediamine (0·54 g., 0·05 mol.) were refluxed in methanolic solution (10 ml.) for 5 minutes. The solution, on cooling, deposited the *quinoxaline* (0·9 g.), m. p. 62°, which separated from methanol (norite) in colourless felted needles, m. p. 62—63° (Found: N, 7·2. $C_{27}H_{36}N_2$ requires N, 7·0%).

γ-Keto-γ-m-methoxyphenylbutyric Acid.—*m*-Anisoyl chloride (b. p. 96—97°/3 mm.; 16·3 g., 0·095 mol.) was treated with benzyl sodioethane-1 : 1 : 2-tricarboxylate (0·1 mol.) in the usual manner. The product, after debenzylation, decarboxylation, and removal of solvent, was boiled with sodium hydroxide (200 ml.; 2N.) for 30 minutes and the cooled solution acidified with excess of sulphuric acid (20N.). The acid (16·35 g., 83%; m. p. 100—102°) crystallised from aqueous alcohol (norite) in long needles, m. p. 110°. The semicarbazone separated slowly from its reaction mixture (aqueous-alcoholic solution) in needles, m. p. 177°. Thompson (*J.*, 1932, 2314) gave m. p. 111° and 177° respectively for the keto-acid and its semicarbazone.

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72. *Experiments on the Synthesis of Carbonyl Compounds. Part III. Addition of Ethyl Acetoacetate to Ethyl Sorbate.*

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Addition of ethyl acetoacetate to ethyl sorbate has been realised and the product (I) reduced and degraded to (±)-7-*keto*-5-*methyloctanoic acid* (III). The structure of (III) has been proved by reduction to (±)-5-*methyloctanoic* acid (IV) which has been synthesised by an independent route.

In connection with another investigation we wished to prepare 7-keto-5-methyloctanoic acid, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH(Me){\cdot}[CH_2]_2{\cdot}CO_2H$. It seemed possible that a convenient method for the preparation of this material was by way of the keto-diester (I) which would result from a Michael addition of ethyl acetoacetate to ethyl sorbate:

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et + CHMe{:}CH{\cdot}CH{:}CH{\cdot}CO_2Et \longrightarrow CH_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CHMe{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2Et \quad (I.)$$

$$(III.)\ CH_3{\cdot}CO{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H \longleftarrow CH_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2Et \quad (II.)$$

There appears to be no recorded instance in the literature of the addition of ethyl acetoacetate to sorbic esters, although malonic and cyanoacetic esters have been used and been found to give products corresponding, predominantly, to 1 : 4-addition (Vorländer, *Annalen*, 1906, **345**, 228; Kohler and Butler, *J. Amer. Chem. Soc.*, 1926, **48**, 1036; Farmer and Healey, *J.*, 1927, 1060; Farmer and Mehta, *J.*, 1930, 1610; Bloom and Ingold, *J.*, 1931, 2765).

In *tert.*-butanolic solution in the presence of potassium *tert.*-butoxide the reaction furnished the unsaturated *keto*-diester (I) in excellent yield. This was catalytically reduced with the aid of palladised strontium carbonate to the corresponding saturated *keto*-diester (II) which on hydrolysis with constant-boiling hydrochloric acid yielded (±)-7-*keto*-5-*methyloctanoic acid* (III), characterised as its *semicarbazone*, p-*bromophenacyl* and *ethyl* ester. The structure and homogeneity of (III) were proved by unequivocal synthesis of the corresponding saturated acid (IV) (p-*bromophenacyl* ester), obtained in almost theoretical yield by the modified Wolff–Kishner reduction (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) and synthesised as follows.

$$\underset{(V.)}{CH_3{\cdot}CO{\cdot}[CH_2]_4{\cdot}Cl} \xrightarrow{PrMgBr} \underset{(VI.)}{CH_3{\cdot}CPr{:}CH{\cdot}[CH_2]_3{\cdot}Cl} \xrightarrow{H_2\text{-}PtO_2} \underset{(VII.)}{CH_3{\cdot}CHPr{\cdot}[CH_2]_4{\cdot}Cl} \xrightarrow[KOH]{KCN-} CH_3{\cdot}CHPr{\cdot}[CH_2]_4{\cdot}CO_2H \quad (IV.)$$

1-Chloropentan-4-one (V) and n-propylmagnesium bromide (cf. Cason, Brewer, and Pippen, *J. Org. Chem.*, 1948, **13**, 239—248) gave *5-methylhept-4-enyl chloride* (VI), separated from unchanged ketone by oximation of the ketone, followed by distillation, and then reduced using Adams's catalyst and treated, without isolation, with potassium cyanide and then sodium hydroxide to give (±)-*5-methyloctanoic acid*, identical with the acid resulting from (III).

The evidence presented herein leaves, in our opinion, no doubt of the homogeneity or structure of (III). For the keto-esters (I) and (II) the position is not so clear, as complete absence of the analogous products formed by 1 : 2-addition cannot be assumed.

Experimental.

Ethyl 6-Keto-5-methylhept-2-ene-1 : 5-dicarboxylate.—Ethyl acetoacetate (98 g., 0·75 mol.) and ethyl sorbate (53 g., 0·38 mol.) were added to absolute *tert.*-butanol (150 ml.) in which potassium (2·5 g.) had been dissolved, and the mixture was refluxed in an oil-bath at 110—120° for 12 hours. The cold solution was poured into dilute sulphuric acid, and the oil taken up in benzene. After removal of the solvent and unreacted materials by distillation, the *ethyl* ester was obtained as an almost colourless oil (78 g., 75%), b. p. 120°/0·5 mm., n_D^{20} 1·4530 (Found: C, 61·9; H, 8·2. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%). It gave a deep-red colour with aqueous-alcoholic ferric chloride and absorbed bromine with great avidity.

Ethyl 6-Keto-5-methylheptane-1 : 5-dicarboxylate (II).—The unsaturated ester (I) (86 g.) was hydrogenated in alcohol in the presence of palladised strontium carbonate (3 g., 12%) until hydrogenation was complete (1 mol.). After removal of catalyst and solvent, the saturated *keto*-diester distilled as a colourless oil, b. p. 118°/0·2 mm., n_D^{20} 1·4479 (Found: C, 61·9; H, 9·2. $C_{14}H_{24}O_5$ requires C, 61·7; H, 8·8%).

7-Keto-5-methyloctanoic Acid (III).—The foregoing ester (69 g.) was refluxed with concentrated hydrochloric acid and water (200 ml. of each) until evolution of carbon dioxide ceased (6 hours). The oil was taken up in benzene, the residue remaining after removal of solvent was refluxed for 2 hours with sodium hydroxide (100 ml.; 5*N*.), and the solution was steam-distilled. Acidification of the residue furnished an oil which was isolated in the usual manner. *7-Keto-5-methyloctanoic acid* was obtained thereby as a viscous oil (33 g., 75%), b. p. 114°/0·1 mm., n_D^{20} 1·4528 (Found: C, 62·8; H, 9·5%; equiv., 173. $C_9H_{16}O_3$ requires C, 62·8; H, 9·4%; equiv., 172). The *p-bromophenacyl ester*, crystallised from aqueous alcohol, had m. p. 60—61° (Found: C, 54·7; H, 5·6. $C_{17}H_{21}O_4Br$ requires C, 55·3; H, 5·7%), and the *semicarbazone* crystallised from ethyl acetate–dioxan in tiny prisms, m. p. 146—147° (Found: N, 17·7. $C_{10}H_{19}O_3N_3$ requires N, 18·3%).

Ethyl 7-Keto-5-methyloctanoate.—A mixture of the acid (55 g.), ethanol (100 ml.), benzene (100 ml.), and sulphuric acid (2 g.) was distilled through a Fenske column fitted with a phase-separator until no further separation took place. The cooled residue was washed with water, sodium hydrogen carbonate solution, and water successively. After removal of solvent, the *ester* was obtained as a colourless oil which distilled at 91—92°/0·5 mm. and had n_D^{20} 1·4362 (62 g., 97%) (Found: C, 65·7; H, 10·0. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·1%).

Wolff–Kishner Reduction of (III).—The foregoing keto-acid (10 g.) was reduced with sodium hydroxide (5 g.), hydrazine hydrate (13 ml.; 60%), and 2 : 2′-dihydroxydiethyl ether (75 ml.) in the manner described by Huang-Minlon (*loc. cit.*), and the reduced acid, (±)-*5-methyloctanoic acid*, isolated as an oil (9 g.), b. p. 150°/30 mm., n_D^{20} 1·4355 (Found: C, 68·1; H, 11·5%; equiv., 158. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%; equiv., 158). The *p*-bromophenacyl ester crystallised from aqueous alcohol in colourless plates, m. p. 46—46·5°, undepressed by admixture with the material prepared synthetically.

Synthesis of (±)-*5-Methyloctanoic Acid*.—1-Chloro-5-methylheptene (VI) was prepared as described by Cason *et al.* (*loc. cit.*) for the higher homologue, using n-propyl bromide (80 g.), magnesium (16 g.), and 1-chloropentan-4-one (80 g.; freshly distilled). The product boiled at 70—73°/22 mm. and contained about 15% of ketone (oxime value). The crude product (41 g.) was thoroughly shaken with a solution of hydroxylamine hydrochloride (20 g.) in water (100 ml.), sufficient sodium hydroxide solution being added from time to time to keep the aqueous solution alkaline to *p*-bromophenol-blue. When no further alkali was needed, the chloro-compound was extracted with benzene. The organic layer was washed with water, dried ($CaCl_2$), and distilled to give the *chloro-olefin* as a colourless, mobile liquid (36 g.), b. p. 72°/22 mm., n_D^{20} 1·4514, possessing an unpleasant odour (Found: C, 65·5; H, 10·3. $C_9H_{17}Cl$ requires C, 65·5; H, 10·2%).

The above chloro-compound (34 g., 0·23 mol.) was hydrogenated in 95% ethanol in the presence of Adams's catalyst (0·2 g.). Absorption of hydrogen was extremely rapid and finally stopped when a total of 6·3 l. had been absorbed (theory, 5·2 l.). After removal of catalyst by filtration, the filtrate was carefully neutralised with 10*N*-sodium hydroxide, the amount of the latter being in accord with that required if the excess of hydrogen was used to displace chlorine as hydrogen chloride. A solution of potassium cyanide (32 g.) in water (50 ml.) was then added to the filtrate containing the saturated chloro-compound together with potassium iodide (5 g.) and ethanol (150 ml.), and the mixture digested on the steam-bath for 30 hours. After cooling, the supernatant liquid was decanted from the solid material which was washed with fresh ethanol (50 ml.). Sodium hydroxide (50 ml.; 10*N*.) was added to the combined alcoholic extracts, and the solution refluxed for a further 30 hours. Water was then added and the mixture steam-distilled to remove a small amount of an evil-smelling material, presumably the isocyanide. Acidification (fume-cupboard) of the residue yielded (±)-5-methyloctanoic acid which was isolated in the usual manner as an oil, b. p. 150°/30 mm., n_D^{20} 1·4355 (Found: C, 68·2; H, 11·5%). The yield of this acid was 24 g. (66% based on chloro-olefin, or 81% if allowance is made for the extra hydrogen consumed during the hydrogenation of the chloro-olefin resulting in the formation of the corresponding paraffin).

The *p*-bromophenacyl ester separated from aqueous alcohol in colourless plates, m. p. 46—46·5° (Found: C, 57·6; H, 6·9. $C_{11}H_{13}O_3Br$ requires C, 57·5; H, 6·5%).

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73. *Isomerisation Reactions. Part III.*

By R. R. AITKEN, G. M. BADGER, and J. W. COOK.

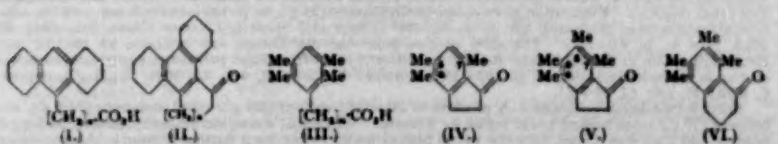
The action of hydrogen fluoride on a series of acids (III; $n = 0, 1, 2, 3$) derived from durene has been investigated. In two cases ($n = 0$ or 1) no reaction occurred. *β-Durylpropionic acid* ($n = 2$) gave a mixture of ketones (IV and V), one formed by elimination of a methyl group and the other by migration. *γ-Durylbutyric acid* ($n = 3$) gave 5 : 6 : 7 : 8-tetramethyl-1-tetralone (VI) by migration of methyl. *β-Pentamethylphenylpropionic acid* reacted with hydrogen fluoride to give (V), with elimination of methyl, whereas *γ-pentamethylphenylbutyric acid* gave no ketonic product.

COMPOUNDS of type (I), in which $n = 2$ or 3, undergo isomerisation and cyclisation on treatment with anhydrous hydrogen fluoride at room temperature, to give derivatives of *s*-octahydrophenanthrene (II) (Badger, Carruthers, Cook, and Schoental, *J.*, 1949, 169; Badger, Carruthers, and Cook, *ibid.*, p. 2044). Cyclisation is evidently essential for isomerisation to occur, for hydrogen fluoride did not isomerise a number of related compounds in which the subsequent cyclisation could not take place. The analogy between this type of isomerisation and that observed with aluminium chloride has already been noted, as well as the analogy to the Jacobsen reaction, in which isomerisations are brought about by concentrated sulphuric acid. In these last two cases, however, cyclisation is not an essential feature, and in this respect, therefore, the isomerisations observed with hydrogen fluoride, at room temperature, appear to be unique. However, the displacement of an alkyl group by an entering acyl group in the preparation of aromatic ketones using aluminium chloride has been reported by Auwers and Mauss (*Annalen*, 1928, **460**, 240), and by Hennion and McLeese (*J. Amer. Chem. Soc.*, 1942, **64**, 2421).

Baddeley (*J.*, 1944, 232) has pointed out that migrations of alkyl groups in benzene homologues, phenols, aryl ketones, and hydroxyaryl ketones by means of aluminium chloride are related to one another and to the Jacobsen reaction. He also distinguishes between two types of aluminium chloride isomerisations, namely (i) the reversible isomerisation of homologues of benzene and phenol associated with intramolecular migrations of alkyl groups to adjacent positions, and (ii) the irreversible isomerisation of aromatic ketones, closely comparable with the Jacobsen reaction, which involve intramolecular migration of alkyl groups to adjacent positions and, alternatively, migration, perhaps intramolecular, of acyl groups. The hydrogen fluoride rearrangements of octahydroanthracene derivatives show some of the features of both types. For this reason, and because most of the work on the Jacobsen reaction has been carried out with polyalkylbenzenes ("Organic Reactions," 1942, Vol. I, p. 370), we have extended our studies with hydrogen fluoride to some derivatives of durene and of pentamethylbenzene.

Durene itself was unaffected by hydrogen fluoride at room temperature, a result which is in agreement with previous work (Calcott, Tinker, and Weinmayr, *J. Amer. Chem. Soc.*, 1939, **61**, 1010), although it is known that hydrogen fluoride isomerises homologues of benzene at high temperatures and pressures (U.S.P. 2,416,184).

Similarly, durenecarboxylic acid and *durylacetic acid* (III; $n = 1$) were recovered unchanged after treatment with hydrogen fluoride, and in this respect, these results are entirely comparable with those observed in the case of octahydroanthracene and its simple derivatives (Badger, Carruthers, and Cook, *loc. cit.*). With *β-durylpropionic acid* (III; $n = 2$), and with *γ-durylbutyric acid* (III; $n = 3$), cyclisation and isomerisation were observed.



Treatment of β-durylpropionic acid with hydrogen fluoride gave a mixture from which 4 : 5 : 7-*trimethylindan*-1-*one* (IV) and 4 : 5 : 6 : 7-*tetramethylindan*-1-*one* (V) were isolated and characterised as the *oximes*. The former ketone is formed by simultaneous cyclisation with the *loss* of a methyl group, and the latter, formed in rather greater amount, by simultaneous cyclisation with *migration* of a methyl group. Similar effects have often been observed in isomerisations with other reagents such as aluminium chloride. The structures of the two ketones were established by oxidation with dilute nitric acid to the corresponding benzenepolycarboxylic acids. Cyclisation and isomerisation of γ-durylbutyric acid proceeded rather more readily, and in better yield, to give only one ketone. This ketone, also characterised as its *oxime*, was oxidised to mellitic acid, and was therefore 5 : 6 : 7 : 8-*tetramethyl*-1-*tetralone* (VI).

β-*Pentamethylphenylpropionic acid* on treatment with hydrogen fluoride gave only one ketone, namely 4 : 5 : 6 : 7-tetramethylindanone (V), formed by cyclisation with elimination of a methyl group. Unexpectedly, the homologous acid, γ-*pentamethylphenylbutyric acid* gave no ketonic product with hydrogen fluoride.

Durenecarboxylic acid was prepared from bromodurene by carboxylation of its magnesio-derivative (Fuson and Kelton, *J. Amer. Chem. Soc.*, 1941, **63**, 1800). Chloromethylation of durene, by a modification of the method used by Nauta and Dienske (*Rec. Trav. chim.*, 1936, **55**, 1000) for mesitylene, gave chloromethyldurene and *bischloromethyldurene*. The former, on interaction with potassium cyanide, followed by hydrolysis of the resulting *cyanomethyldurene*, gave durylacetic acid (III; $n = 1$). Condensation of chloromethyldurene with ethyl sodiomalonate gave *ethyl durylmethylmalonate*, which on hydrolysis to the *acid* followed by decarboxylation gave β-durylpropionic acid (III; $n = 2$). Chain lengthening by the Arndt–Eistert procedure gave, through the *amide*, γ-durylbutyric acid (III; $n = 3$). β-Pentamethylphenylpropionic acid and γ-pentamethylphenylbutyric acid were obtained from pentamethylbenzene by exactly similar routes. The former was also prepared by chloromethylation of β-durylpropionic acid followed by catalytic hydrogenation of the *chloromethyldurylpropionic acid* so formed.

The Friedel–Crafts reaction between durene and succinic anhydride in presence of aluminium chloride has also been investigated. In carbon disulphide solution this gave a mixture from which the normal product, γ-*keto*-γ-*durylbutyric acid*, m. p. 160°, was isolated with difficulty, together with the isomeric γ-*keto*-γ-*prehnitylbutyric acid*, m. p. 107°. Under these conditions Muhr (*Ber.*, 1895, **28**, 3217) claimed to have prepared γ-keto-γ-durylbutyric acid, m. p. 117°. This was evidently a mixture. When the reaction was carried out in tetrachloroethane solution γ-keto-γ-durylbutyric acid was more readily obtained pure, its isomer being formed in only small amount. This solvent influence is somewhat similar to that observed by Badger, Carruthers, and Cook (*loc. cit.*) in the corresponding reaction of *s*-octahydroanthracene and succinic anhydride. These authors found that in tetrachloroethane a mixture of keto-acids was formed, whereas the use of carbon disulphide led to more complete isomerisation to octahydrophenanthroylpropionic acid.

Reduction of γ-keto-γ-durylbutyric acid to γ-durylbutyric acid (III; $n = 3$) was difficult, presumably on account of steric hindrance. It was not effected by hydrazine hydrate at 195°, and although the Clemmensen method yielded a small amount of the desired acid much of the keto-acid was unchanged.

Experimental.

Durene.—Durene was prepared by bischloromethylation of technical xylene, followed by reduction of the bischloromethyl compound with zinc and sodium hydroxide solution (von Braun and Nelles, *Ber.*, 1934, **67**, 1094). Reduction by catalytic hydrogenation in acetone, over palladised asbestos, gave a theoretical yield in small-scale (2-g.) runs, but on a large scale the reduction was tediously long and tended to give incompletely reduced material. Durene was recovered unchanged after treatment, for 36 hours, with anhydrous hydrogen fluoride at room temperature.

Chloromethyldurene.—A mixture of durene (22 g.), glacial acetic acid (30 c.c.), concentrated hydrochloric acid (110 c.c.), and aqueous formaldehyde (40%; 10·7 g.) was heated at 70°, for 6 hours, a further quantity (4·4 g.) of formaldehyde being added after 3 hours. After cooling, the aqueous layer was decanted, and the solid dissolved in benzene, washed with sodium carbonate solution and then water, and dried (K_2CO_3). Distillation gave chloromethyldurene (22 g.), b. p. 139—141°/15 mm., which, after crystallisation from methanol, had m. p. 65—66° (Fuson and Sperati, *J. Amer. Chem. Soc.*, 1941, **63**, 2643, give m. p. 67—68°). The solid residue from the distillation was sublimed at 160°/15 mm. Recrystallisation of the sublimate (3—5 g. in different runs) from light petroleum gave *bischloromethyldurene* as colourless needles, m. p. 193—194° (Found: C, 62·0; H, 6·8; Cl, 30·5. $C_{12}H_{16}Cl_2$ requires C, 62·3; H, 7·0; Cl, 30·7%).

Ethyl β-Durylmethylmalonate.—A mixture of atomised sodium (3·5 g.), ethyl malonate (24·2 g.), and benzene (75 c.c.) was heated under reflux for 3 hours. While still warm, chloromethyldurene (25·2 g.) in benzene (40 c.c.) was added, and the whole heated under reflux for a further 2 hours. After cooling,

the mixture was poured into water, and the benzene layer separated, washed, and dried. Fractional distillation gave chloromethyldurene, ethyl malonate, and *ethyl β-durylmethylmalonate*, b. p. 158—160°/0·5 mm. (31 g.), which crystallised from light petroleum in colourless prisms, m. p. 58—59° (Found: C, 70·5; H, 8·6. $C_{18}H_{26}O_4$ requires C, 70·6; H, 8·6%). Hydrolysis with aqueous-ethanolic potassium hydroxide for 3 hours gave *β-durylmethylmalonic acid*, which crystallised from water as colourless plates, m. p. 176° (with evolution of carbon dioxide) (Found: C, 67·4; H, 6·9. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

β-Durylpropionic Acid (III; $n = 2$).—The above malonic acid (2 g.) was heated in an oil-bath at 180°, until evolution of gas ceased. *β-Durylpropionic acid* (1·5 g.) formed needles, m. p. 170°, from benzene or aqueous acetic acid (Found: C, 75·6; H, 8·6. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%). *β-Durylpropionamide* crystallised from ethanol in needles, m. p. 201—202° (Found: C, 76·2; H, 9·0; N, 7·0. $C_{13}H_{19}ON$ requires C, 76·1; H, 9·3; N, 6·8%).

Isomerisation and Cyclisation of β-Durylpropionic Acid.—The above acid (2 g.) was allowed to stand with excess of anhydrous hydrogen fluoride for 36 hours. The resulting dark residue was poured on ice and extracted with ether. Extraction of the ethereal solution with dilute sodium carbonate solution, followed by acidification of the extract, gave unchanged acid (1·4 g.) identified by m. p. and mixed m. p. The ethereal solution yielded a brown oil (0·5 g.), which solidified when kept. After purification by passage of its solution in benzene through a column of alumina, the product was obtained as a pale yellow solid which separated from light petroleum as a mixture of ketone-A (needles) and ketone-B (prisms), which were separated mechanically.

Purification of ketone-A by recrystallisation from light petroleum, gave 4 : 5 : 7-*trimethylindan*-1-*one* (IV) as colourless needles, m. p. 104—105° [Found: C, 82·5; H, 8·1%; *M* (Rast), 199. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%; *M*, 174]. The *oxime* formed colourless plates, m. p. 223—224° (decomp.), from benzene–light petroleum (Found: C, 76·3; H, 7·8; N, 7·35. $C_{12}H_{15}ON$ requires C, 76·1; H, 8·0; N, 7·4%). Hydrolysis of the oxime with dilute hydrochloric acid in boiling ethanol regenerated the ketone, of unchanged m. p. For oxidation, the ketone (0·12 g.) was heated at 175—180° in a sealed tube, for 6 hours, with water (2 c.c.) and concentrated nitric acid (1 c.c.). Evaporation to dryness and esterification of the residue with excess of ethereal diazomethane gave methyl benzenepentacarboxylate, m. p. 145—146°, not depressed on admixture with an authentic specimen prepared in a similar manner by oxidation of pentamethylbenzene (*cf.* Cook and Hewett, *J.*, 1934, 371; Fieser and Joshel, *J. Amer. Chem. Soc.*, 1940, **62**, 1213).

Purification of ketone-B by recrystallisation from light petroleum (charcoal) gave 4 : 5 : 6 : 7-*tetramethylindan*-1-*one* (V) as colourless plates, m. p. 149—150° [Found: C, 82·8; H, 8·6%; *M* (Rast), 172. $C_{13}H_{16}O$ requires C, 82·9; H, 8·6%; *M*, 188]. The m. p. was unchanged when the ketone was purified through its *oxime*, which crystallised from ethanol in small needles, m. p. 211—212° (Found: C, 77·0; H, 8·4; N, 7·2. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·4; N, 6·9%). Oxidation of tetramethylindanone with dilute nitric acid, as described above for trimethylindanone, gave methyl mellitate, m. p. 186—187°, from methanol, not depressed by admixture with an authentic specimen, m. p. 187—188°.

γ-Keto-γ-duryl- and γ-Keto-γ-prehnityl-butyric Acid.—To a stirred ice-cold suspension of aluminium chloride (10 g.) in carbon disulphide (30 c.c.), a solution of durene (3·3 g.) and succinic anhydride (2·5 g.) in carbon disulphide (30 c.c.) was added dropwise, during 30 minutes. After being stirred for 4 hours at 0° and then 8 hours at room temperature, the mixture was set aside, without stirring, for a further 16 hours. The acidic product (3·2 g.) had m. p. 117—134°, and was purified by crystallisation from ethanol, followed by crystallisation of the sodium salt from water. *γ-Keto-γ-durylbutyric acid*, obtained from the purified sodium salt, formed colourless prisms, m. p. 160—161°, from ethanol (Found: C, 71·5; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). Durene was regenerated when this acid was heated with concentrated hydrochloric acid in a sealed tube at 150° for 6 hours. The *p-nitrobenzyl* ester crystallised from methanol in plates, m. p. 120—121° (Found: C, 68·3; H, 6·4; N, 3·5. $C_{21}H_{23}O_5N$ requires C, 68·3; H, 6·3; N, 3·8%).

The same acid was isolated following interaction of durene and succinic anhydride with aluminium chloride, in tetrachloroethane solution.

The acid recovered from the mother-liquors of the sodium salt was crystallised from aqueous ethanol and then benzene–hexane, and gave *γ-keto-γ-prehnitylbutyric acid*, m. p. 107—108° (Found: C, 71·6; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). This acid (0·1 g.) was added to ice-cold 10% sodium hypobromite solution (10 c.c.), and the suspension gradually heated to 100°, with occasional shaking (2 hours). The mixture was maintained at 100° for 3 hours and filtered hot. Acidification gave prehnitenecarboxylic acid, m. p. 165—166°, from ligroin (lit., m. p. 168—169°), and the amide prepared from it had m. p. 220° (lit., m. p. 222°).

γ-Durylbutyric Acid (III; $n = 3$).—(*a*) A mixture of β-durylpropionic acid (III; $n = 2$) (2 g.), thionyl chloride (2·5 c.c.), benzene (15 c.c.), and pyridine (1 drop) was refluxed for 2 hours. The benzene and excess of thionyl chloride were then removed in a vacuum, and the residue was evaporated with two portions (10 c.c. each) of benzene. The residue was then dissolved in benzene (20 c.c.) and added gradually, with stirring, to an ice-cold solution of diazomethane (from 7 g. of nitrosomethylurea) in ether (120 c.c.). The resulting solution was evaporated to dryness in a stream of dry air, and the residue, in dioxan (20 c.c.), was refluxed for 2½ hours with a solution of 10% silver nitrate (3 c.c.) and 20% ammonia (15 c.c.). The resulting mixture was filtered hot, the residue on the paper was washed with hot dioxan, and the combined solutions were poured into water. *γ-Durylbutyramide* (1·05 g.) crystallised from ethanol in colourless plates, m. p. 171—172° (Found: C, 76·8; H, 9·5; N, 6·1. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·7; N, 6·4%). Hydrolysis of the amide (1 g.) was effected by 10 hours' refluxing with potassium hydroxide (5 g.) in ethanol (50 c.c.). *γ-Durylbutyric acid* (III; $n = 3$) (0·89 g.) crystallised from benzene, and then from *cyclo*hexane, in colourless plates, m. p. 139—140° (Found: C, 76·2; H, 9·0. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%).

(*b*) An attempt to prepare durylbutyric acid by reduction of γ-keto-γ-durylbutyric acid by the modified Kishner–Wolff procedure (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) was unsuccessful, only unchanged material being isolated. Reduction by the Clemmensen method was, however, partly successful. A mixture of γ-keto-γ-durylbutyric acid (1·5 g.), toluene (15 c.c.), acetic acid (10 c.c.),

concentrated hydrochloric acid (75 c.c.), and amalgamated zinc (10 g.) was refluxed for 48 hours. Additions of zinc (total, 15 g.) and of hydrochloric acid (total, 75 c.c.) were made at intervals. The product, m. p. 114—130°, was purified by conversion into the sodium salt, and separation into soluble and sparingly soluble fractions. Acidification of the sparingly soluble salt gave unchanged keto-acid (1·0 g.), identified by m. p. and mixed m. p. Acidification of the soluble salt, followed by recrystallisation of the product from *cyclo*hexane, gave γ-durylbutyric acid (0·27 g.), m. p. 138—139°, identical with that obtained as under (*a*).

Isomerisation and Cyclisation of γ-Durylbutyric Acid (III; n = 3).—γ-Durylbutyric acid (1 g.) was set aside in excess of anhydrous hydrogen fluoride for 36 hours. The resulting brown residue was poured on ice and extracted with ether. Extraction of the ethereal solution with dilute sodium carbonate solution, followed by acidification of the extract, gave unchanged acid (0·38 g.), identified by m. p. and mixed m. p. Evaporation of the ethereal solution gave a slightly coloured solid residue which on crystallisation from ethanol (twice) gave 5 : 6 : 7 : 8-*tetramethyl*-1-*tetralone* (VI) as colourless needles, m. p. 106—107° [Found : C, 83·4; H, 9·2%; *M* (Rast), 200. $C_{14}H_{18}O$ requires C, 83·1; H, 9·0%; *M*, 202]. The *oxime* formed colourless needles, m. p. 185—186°, from ethanol (Found : C, 77·15; H, 8·6; N, 6·6. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8; N, 6·45%). The oxime (0·05 g.), hydrolysed as described above for trimethylindanone, yielded after crystallisation from ethanol the ketone of the same m. p. Oxidation of this ketone (VI) with dilute nitric acid as described above for trimethylindanone yielded methyl mellitate, m. p. 185—187°, from methanol, not depressed on admixture with an authentic specimen.

Durenecarboxylic Acid.—This was obtained from the bromo-derivative by interaction with magnesium in dry ether, followed by carboxylation with solid carbon dioxide. It crystallised from light petroleum in colourless plates, m. p. 178°. Fuson and Kelton (*J. Amer. Chem. Soc.*, 1941, **63**, 1500) give m. p. 179—180°. It was recovered unchanged after being kept in anhydrous hydrogen fluoride, at room temperature, for 48 hours.

Durylacetic Acid.—Potassium cyanide (5 g.) in water (9 c.c.) was added to chloromethyldurene (2 g.) in ethanol (25 c.c.), and the mixture was boiled under reflux for 2 hours. The cooled solution was added to a large excess of water. The precipitated *cyanomethyldurene* formed needles, m. p. 84—85° (from aqueous methanol), after distillation (b. p. 168°/20 mm.) (Found : C, 83·3; H, 8·5; N, 8·3. $C_{13}H_{17}N$ requires C, 83·2; H, 8·7; N, 8·1%). Hydrolysis of the crude cyanide, by boiling with a mixture of equal volumes of sulphuric acid, water, and acetic acid, gave *durylacetic acid* which crystallised from benzene in colourless plates, m. p. 198—199° (Found : C, 75·2; H, 8·1. $C_{13}H_{18}O_2$ requires C, 75·0; H, 8·4%). Durylacetic acid was recovered unchanged after treatment with hydrogen fluoride, at room temperature, for 48 hours.

Pentamethylbenzene.—Pentamethylbenzene was prepared by bischloromethylation of mesitylene (Nauta and Dienske, *Rec. Trav. chim.*, 1936, **55**, 1000), followed by reduction of the bischloromethyl compound. Several methods were investigated in an attempt to accomplish this reaction. Reduction by catalytic hydrogenation with palladised asbestos in acetone, though efficient in small scale runs (2 g.) as with dichloromethylxylene, was found to be tediously long and to give incompletely reduced products. Reduction with zinc and aqueous alcohol (*cf.* Hewett, *J.*, 1940, 298) gave mainly non-crystalline undistillable products, as did reduction with nickel–aluminium alloy and aqueous sodium hydroxide, at about 90°. The reduction was most readily accomplished by stirring the bischloromethylmesitylene, in toluene, with zinc and aqueous sodium hydroxide. When benzene was used in place of toluene, as described by von Braun and Nelles (*Ber.*, 1934, **67**, 1094) for the reduction of bischloromethylxylene, the yield of pentamethylbenzene was considerably reduced.

Pentamethylbenzene was also obtained by shaking chloromethyldurene (10 g.) in acetone (150 c.c.) with hydrogen at ordinary pressures and temperatures in presence of palladium on asbestos as catalyst. Reduction was complete within 3½ hours.

Pentamethylchloromethylbenzene.—A mixture of pentamethylbenzene (14 g.), concentrated hydrochloric acid (70 c.c.), and aqueous formaldehyde (7 g.; 40%) was stirred while being heated at 65° for 6 hours, a further quantity (2·5 g.) of formaldehyde being added after 3 hours. After cooling, the aqueous layer was decanted and the semi-solid residue dissolved in benzene, washed with sodium carbonate solution and then with water, and dried (K_2CO_3). Distillation yielded *pentamethylchloromethylbenzene* (12 g.), b. p. 148°/14 mm., which crystallised from light petroleum in prisms, m. p. 82—84° (Found : C, 73·05; H, 8·8; Cl, 17·9. $C_{12}H_{17}Cl$ requires C, 73·3; H, 8·7; Cl, 18·0%). Pentamethylchloromethylbenzene was also obtained, though mixed with hexamethylbenzene, by treating hexamethylbenzene with phosphorus pentachloride as described by Jacobsen (*Ber.*, 1889, **22**, 1217), who claims to have obtained pentamethylchloromethylbenzene, m. p. 99°, by this method.

Ethyl Pentamethylbenzylmalonate.—A mixture of atomised sodium (1·7 g.), ethyl malonate (11·6 g.), and benzene (50 c.c.) was heated under reflux for 3 hours. Whilst still warm, pentamethylchloromethylbenzene (12 g.) in benzene (20 c.c.) was added, and the whole heated under reflux for a further 2 hours. The cooled mixture was then poured into water, and the benzene layer separated, washed, and dried. Distillation gave *ethyl pentamethylbenzylmalonate*, b. p. 177—180°/1·5 mm. (14·5 g.), which crystallised from ethanol in needles, m. p. 71—73° (Found : C, 71·2; H, 8·9. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%). Hydrolysis of the ester (14·5 g.) with aqueous-ethanolic potassium hydroxide for 2 hours gave *pentamethylbenzylmalonic acid* (9·4 g.), which formed plates, m. p. 191·5° (with evolution of carbon dioxide), from aqueous ethanol (3 : 1) (Found : C, 68·45; H, 7·8. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

β-Pentamethylphenylpropionic Acid.—The malonic acid (9·4 g.) was heated in an oil-bath at 195° till evolution of gas had ceased. *β-Pentamethylphenylpropionic acid* (6·4 g.) formed needles, m. p. 175—176°, from benzene (Found : C, 76·2; H, 9·3. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%).

This acid was also obtained as follows. A mixture of β-durylpropionic acid (2 g.), aqueous formaldehyde (1·5 g.; 40%), and concentrated hydrochloric acid (20 c.c.) was stirred for 6 hours whilst being heated at 80°. After 3 hours a further quantity (1·0 g.) of formaldehyde was added. The cooled mixture was added to water and filtered. *β-Chloromethyldurylpropionic acid* formed needles, m. p. 216—218°, from dioxan (Found : C, 66·2; H, 7·45; Cl, 14·1. $C_{14}H_{19}O_2Cl$ requires C, 66·0; H, 7·5; Cl, 13·9%).

β-Acetoxymethyldurylpropionic acid, prepared from this by warming it with sodium acetate in acetic acid to 100° for 30 minutes, formed long fine needles, m. p. 203—204°, from aqueous acetic acid (Found: C, 69·0; H, 8·0. $C_{15}H_{22}O_4$ requires C, 69·0; H, 8·0%). *β-Hydroxymethyldurylpropionic acid*, prepared by sodium carbonate hydrolysis of either of the above two acids, formed large firm needles, m. p. 213—214° with evolution of gas (from ethyl acetate) (Found: C, 71·4; H, 9·4. $C_{13}H_{20}O_3$ requires C, 71·15; H, 8·5%).

One run of the chloromethylation reaction, when acetic acid was present, yielded β-acetoxymethyldurylpropionic acid; its identity was shown by m. p. and mixed m. p. with a specimen prepared as described above and by hydrolysis with sodium carbonate to β-hydroxymethyldurylpropionic acid.

Chloromethyldurylpropionic acid (0·3 g.) in acetone (15 c.c.) was shaken with hydrogen at ordinary temperature and pressure in presence of palladium-black. Reduction was complete in 2 hours. The filtered residue yielded *β-pentamethylphenylpropionic acid*, m. p. 172—174°, not depressed by mixture with the specimen prepared as described above.

Isomerisation and Cyclisation of β-Pentamethylphenylpropionic Acid.—The acid (1 g.) was left in contact with excess of anhydrous hydrogen fluoride for 36 hours. The resulting brown oil was poured on ice and extracted with ether. Extraction of the ethereal solution with sodium carbonate solution followed by acidification of the alkaline extract gave unchanged acid (0·37 g.). The ethereal solution yielded a brown oil (0·54 g.) which solidified in an ice-bath. After purification by passage of its benzene solution through a column of alumina the product, a pale yellow solid, was crystallised from light petroleum. It formed plates, m. p. 150—152°, not depressed by admixture with tetramethylindanone (V). Identification was completed by preparation of the oxime, m. p. 213—214°.

γ-Pentamethylphenylbutyric Acid.—A mixture of β-pentamethylphenylpropionic acid (2·2 g.), thionyl chloride (2·75 c.c.), benzene (15 c.c.), and pyridine (1 drop) was refluxed for 2 hours. The benzene and excess of thionyl chloride were removed *in vacuo*, and the residue was evaporated with 2 portions (10 c.c. each) of dry benzene. The residue in benzene (20 c.c.) was added with stirring to an ice-cold solution of diazomethane (from 8 g. of nitrosomethylurea) in ether (150 c.c.). The resulting mixture, from which part of the diazoketone could be crystallised by cooling it in ice, was evaporated to dryness in a stream of dry air, and the residue, dissolved in dioxan (25 c.c.), was refluxed for 2½ hours with a solution of silver nitrate (3 c.c.; 10%) and ammonia (15 c.c.; 20%). The resulting mixture was filtered hot, the residue on the paper was washed with hot ethanol, and the combined solutions were poured into water. *γ-Pentamethylphenylbutyramide* (1·15 g.) formed very small needles, m. p. 185—186°, from benzene (Found: C, 77·4; H, 10·2; N, 6·4. $C_{15}H_{23}ON$ requires C, 77·2; H, 9·9; N, 6·0%). Hydrolysis of the amide (1·15 g.) was effected by refluxing it for 10 hours with potassium hydroxide (5 g.) in ethanol (50 c.c.). *γ-Pentamethylphenylbutyric acid* (0·75 g.) formed plates, m. p. 157—158°, from benzene (Found: C, 76·8; H, 9·4. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%). When this acid was left in contact with excess of hydrogen fluoride for 36 hours it was recovered entirely unchanged.

One of us (G. M. B.) has held an I.C.I. Research Fellowship during this investigation. We are also indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance (to R. R. A.). Microanalyses were carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW. [*Received, October 26th*, 1949.]

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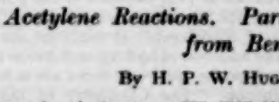
74. *Acetylene Reactions. Part VII. Acetylenic Amino-alcohols from Benzophenones.*

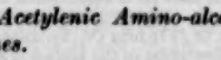
By H. P. W. HUGGILL and J. D. ROSE.

Compounds of the type $CPh_2(OH)\cdot C{\equiv}C\cdot CHR\cdot NR'_2$ and their semi- and completely hydrogenated analogues have been prepared for test as spasmolytics. Two methods have been used: (*a*) when R = CH_3, by interaction of 3-alkylamino- and 3-dialkylamino-but-1-ynes with benzophenones; and (*b*), when R = H, from diphenylethynylcarbinol or its acetate, formaldehyde, and a secondary amine. Some reactions of these compounds, particularly their hydrogenation, addition of hydrogen chloride, and Meyer–Schuster rearrangement with sulphuric acid, are described.

As part of a general programme of work on spasmolytic substances, unsaturated derivatives of diphenylcarbinol were required containing a basic substituent in the unsaturated side chain. Substances of type (I) and their ethylenic analogues, which have some structural similarity to "Trasentin" (II) (Meier and Salow, *Klin. Wochenschr.*, 1936, **15**, 1403, 1405), "Aspasin" (III) (B.I.O.S. Final Report No. 116, p. 57), and the 3-dialkylamino-1:1-diphenylpropanols (IV) (Roche Products Ltd., B.P. 615,136), seemed to be most readily accessible.



(I.)



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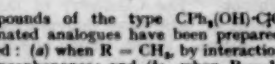

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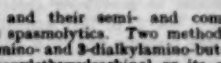


(IV.)

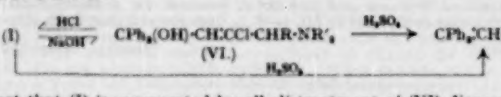
Two routes were used for the preparation of these compounds. The first was based on the availability of the 3-alkylamino- and 3-dialkylamino-but-1-ynes (Part I of this series, *J.*, 1949, 780) which condensed readily with benzophenone in the presence of alkali to give the required acetylenic amino-alcohols. This reaction was not completely general, and failed with 4 : 4'-bisdimethylaminobenzophenone (Michler's ketone).

The second route involved the Mannich reaction of diphenylethynylcarbinol (from benzophenone and acetylene), formaldehyde, and the secondary amine. In this reaction it was found advantageous to acetylate the carbinol before carrying out the Mannich condensation, as otherwise very low yields were obtained. It is noteworthy that during the Mannich condensation the acetyl group was lost and the resulting amino-acetylenic alcohols could not subsequently be reacetylated. This failure is not unexpected, since not only is the hydroxyl group tertiary, but the molecule contains in addition a strongly basic group and is too unstable to acid reagents to permit very drastic acetylation conditions.

The loss of the acetyl group during the Mannich reaction is more surprising. Judged by the difference in reactivity between the carbinol and its acetate in this reaction, it would appear that deacetylation does not precede the Mannich reaction, and the use of morpholine hydrochloride in place of the free base did not prevent deacetylation. The higher yield obtained from the acetate than from the carbinol is in accord with the findings of Jones, Marszak, and Bader (*J.*, 1947, 1578).

The acetylenic amino-alcohols underwent catalytic reduction to either the ethylenic or the saturated analogues, although there was considerable variation in the ease of reduction beyond the ethylenic stage. Those alcohols derived from the 3-dialkylamino- and 3-alkylamino-but-1-ynes (I; R = Me) tended to split off the amino-group in the second stage of the reduction, and attempted saturation of 4-morpholino-1 : 1-diphenylpent-2-yn-1-ol caused complete disruption of the molecule. Amines of the type (I; R = H) were easier to reduce and the reduction products were stable.

With sulphuric acid the 4-dialkylamino-1 : 1-diphenylpent-2-yn-1-ols underwent the Meyer–Schuster rearrangement to 4-dialkyamino-1 : 1-diphenylpent-1-en-3-ones (V), but with hydrochloric acid simple adducts (VI) of the acetylenic amines with HCl were obtained which on treatment with alkali regenerated the original amine and with sulphuric acid gave the αβ-unsaturated ketones.



The fact that (I) is regenerated by alkali treatment of (VI) disposes of the possibility that the hydrogen chloride adducts might be those of the αβ-unsaturated ketone (V), and the conversion of (VI) into (V) by dilute sulphuric acid considerably strengthens the probability that the orientation of the adduct is as shown. The addition of hydrogen chloride to acetylenic amines does not appear to have been recorded previously, although there are a few examples of its addition to acetylenic carbinols (see Johnson, "The Chemistry of the Acetylenic Compounds," Vol. I, p. 101, Arnold, 1946); in most of these cases dehydration to a vinylacetylene was possible and may have preceded addition. Where simple addition occurred, the position of the halogen was not determined.

Experimental.

The 3-alkylamino- and 3-dialkylamino-but-1-ynes used in this work were prepared by the methods of Part I of this series (*loc. cit.*).

4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol.—A solution of benzophenone (175 g.) and 3-diethylaminobut-1-yne (105 g.) in ether (200 c.c.) was added during one hour to a stirred suspension of powdered potassium hydroxide (180 g.) in dry ether (700 c.c.) at 15—20°. After 16 hours' stirring, water (1 l.) was added, and the mixture filtered, giving 97 g. of crude amine (32% based on the dimethylaminobutyne). The ethereal layer from the filtrate was shaken with 1·5*N*-hydrochloric acid (1 l.) which gave, after filtration, 80 g. (24%) of the base hydrochloride. From the filtrates 49 g. of benzophenone and 36 g. of unchanged 3-dimethylaminobut-1-yne were recovered. When crystallised from methyl alcohol, *4-dimethylamino-1 : 1-diphenylpent-2-yn-1-ol* formed white plates, m. p. 144—146° (Found: C, 82·1; H, 7·2; N, 5·3. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5; N, 5·0%). The *methiodide* formed white plates (from methyl alcohol), m. p. 223° (decomp.; bath pre-heated to 205°) (Found: C, 57·0; H, 5·8; N, 3·3. $C_{20}H_{24}ONI$ requires C, 57·0; H, 5·7; N, 3·3%). The *hydrochloride*, white needles from aqueous alcohol, had m. p. 189° (decomp.; bath pre-heated to 180°) (Found: C, 66·8; 66·8; H, 6·8; 7·3; N, 4·25. $C_{19}H_{21}ON,HCl,1·5H_2O$ requires C, 66·6; H, 7·3; N, 4·1%). Attempts to form the acetate with acetyl chloride in pyridine were unsuccessful.

4-*Morpholino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol*.—3-Morpholinobut-1-yne (21 g.) and benzophenone (27·2 g.) were brought into reaction with potassium hydroxide powder (27 g.) in ether (120 c.c.) as described above for the dimethylamino-analogue. The *amino-alcohol* (17 g., 35%) was obtained as white plates, m. p. 142—144°, from methyl alcohol (Found: C, 78·6; H, 7·1; N, 4·55. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·1; N, 4·35%). The *methiodide* formed white needles, m. p. 202—203° (decomp.), from methyl alcohol (Found: C, 56·6; H, 5·8; N, 3·0. $C_{22}H_{26}O_2NI$ requires C, 57·0; H, 5·6; N, 3·0%). The *hydrochloride* formed white plates, m. p. 156° (decomp.; bath preheated to 175°), from methyl alcohol (Found: C, 67·2; H, 6·9; N, 3·6. $C_{21}H_{23}O_2N,HCl,H_2O$ requires C, 67·2; H, 6·9; N, 3·7%). No acetyl derivative could be prepared.

4-*Diethylamino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol*.—A solution of benzophenone (180 g.) and 3-diethylaminobut-1-yne (120 g.) in ether (250 c.c.) was added during one hour to a stirred suspension of powdered potassium hydroxide (180 g.) in dry ether (750 c.c.) at 15—20°. After 16 hours' stirring, water (1 l.) was added, and the ethereal layer separated and extracted with water (1 l.) containing concentrated hydrochloric acid (150 c.c.). The aqueous layer was made strongly alkaline with 10*N*-sodium hydroxide and extracted with ether. Distillation of the dried ethereal solution gave 53 g. (44%) of unchanged diethylaminobutyne and a residue (135 g.) of **4-*diethylamino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol***, which after crystallisation from light petroleum (b. p. 60—80°) formed white prisms m. p. 81—82° (Found: C, 81·7; H, 7·6; N, 4·35. $C_{21}H_{25}ON$ requires C, 82·1; H, 8·1; N, 4·55%). The *methiodide* formed white needles, m. p. 183°, from water (Found: C, 58·6; H, 5·75; N, 3·0. $C_{22}H_{28}ONI$ requires C, 58·9; H, 6·24; N, 3·1%). The *hydrochloride* formed white needles, m. p. 178° (decomp.), from dioxan (Found: N, 3·9. $C_{21}H_{25}ON,HCl$ requires N, 4·0%). No acetyl derivative could be obtained.

4-*Diethylamino*-1 : 1-*di*-p-*tolylpent*-2-*yn*-1-*ol*.—Di-*p*-tolyl ketone (5 g.), 3-diethylaminobut-1-yne (5 g.), and powdered potassium hydroxide (5 g.) were caused to interact as above in ether (50 c.c.) for 48 hours to give the *amino-alcohol* (2·0 g.) as white prisms, m. p. 85°, from light petroleum (b. p. 60—80°) (Found: C, 82·1; H, 8·35; N, 3·7. $C_{23}H_{29}ON$ requires C, 82·4; H, 8·7; N, 4·2%). The *methiodide* formed white prisms (from ethyl alcohol), m. p. 183—185° (decomp.) (Found: C, 60·6; H, 6·8; N, 2·7. $C_{24}H_{32}ONI$ requires C, 60·4; H, 6·7; N, 2·9%).

4-*Diethylamino*-1-*phenyl*-1-p-*tolylpent*-2-*yn*-1-*ol*.—This was prepared from 3-diethylaminobut-1-yne (16 g.), phenyl *p*-tolyl ketone (25 g.), and powdered potassium hydroxide in the usual manner. The *amino-alcohol* formed white prisms, m. p. 66—67°, from light petroleum (b. p. 60—80°) (Found: C, 82·2; H, 8·3; N, 4·2. $C_{22}H_{27}ON$ requires C, 82·2; H, 8·4; N, 4·4%). The *methiodide* formed white prisms (from alcohol), m. p. 212—214° (decomp.; bath preheated to 205°) (Found: C, 59·1; H, 6·5. $C_{23}H_{30}ONI$ requires C, 59·5; H, 6·5%). The *hydrochloride* formed white needles, m. p. 175° (decomp., bath preheated to 165°), from water (Found: C, 72·5; H, 7·8. $C_{22}H_{27}ON,HCl,0·5H_2O$ requires C, 72·05; H, 7·8%).

4-iso*Propylamino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol*.—Similarly prepared from benzophenone (30 g.), 3-*iso*propylaminobut-1-yne (20 g.), and potassium hydroxide (30 g.), this *amino-alcohol* formed white prisms, m. p. 79—80°, from light petroleum (b. p. 60—80°) (Found: C, 82·0; H, 7·8; N, 4·95. $C_{20}H_{23}ON$ requires C, 81·9; H, 7·8; N, 4·8%). The *hydrochloride* formed white needles, m. p. 180°, from acetone (Found: N, 4·1. $C_{20}H_{23}ON,HCl$ requires N, 4·2%). The *N-acetyl* derivative, white needles from *cyclo*hexane, has m. p. 98—99° (Found: C, 78·65; H, 7·5; N, 4·65. $C_{22}H_{25}O_2N$ requires C, 78·8; H, 7·5; N, 4·2%).

4-*Diethylamino*-1-*phenyl*-1-p-*methoxyphenylpent*-2-*yn*-1-*ol*.—*p*-Methoxybenzophenone (18 g.), 3-diethylaminobut-1-yne (12 g.), and potassium hydroxide (15 g.), when similarly interacting in ether (75 c.c.), gave an oil (11 g.) which crystallised when set aside at 0° for 7 days. After recrystallisation from light petroleum (b. p. 40—60°) the *amino-alcohol* was obtained as white prisms, m. p. 50—52° (Found: C, 78·6; H, 8·3; N, 3·9. $C_{23}H_{27}O_2N$ requires C, 78·3; H, 8·0; N, 4·2%). The *methiodide* formed white prisms, m. p. 152—153°, from acetone (Found: C, 57·1; H, 6·35; N, 2·5. $C_{24}H_{30}O_2NI$ requires C, 57·6; H, 6·3; N, 2·9%).

4-*Diethylamino*-1 : 1-*di*-p-*methoxyphenylpent*-2-*yn*-1-*ol*.—This was prepared in the usual way from *pp'*-dimethoxybenzophenone (5 g.), 3-diethylaminobut-1-yne (5 g.), and potassium hydroxide (5 g.). The *amino-alcohol* was obtained as white prisms, m. p. 100°, from light petroleum (b. p. 60—80°) (Found: C, 75·15; H, 7·7; N, 4·1. $C_{23}H_{29}O_3N$ requires C, 75·2; H, 7·9; N, 3·8%).

Diphenylethynylcarbinyl Acetate.—Diphenylethynylcarbinol (20 g.; Campbell, Cambell, and Eby, *J. Amer. Chem. Soc.*, 1938, **60**, 2882) was dissolved in dry pyridine (20 c.c.), and acetyl chloride (8 g.) added dropwise with stirring and cooling. After being kept at 40—50° for 3 hours, the mixture was poured into ice and water (200 g.), and the product extracted with ether and washed with dilute hydrochloric acid (twice) and water. The dried ($MgSO_4$) ethereal solution was distilled, giving 5 g. of an oil, b. p. 120°/1 mm., which solidified when kept for 14 days at 0° and recrystallised from *cyclo*hexane to give colourless prisms of *diphenylethynylcarbinyl acetate*, m. p. 79—80° (Found: C, 81·65; H, 5·5. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

4-*Morpholino*-1 : 1-*diphenylbut*-2-*yn*-1-*ol*.—(a) *From diphenylethynylcarbinyl acetate.* The acetate (30 g.), paraformaldehyde (5 g.), morpholine (12 g.), and dioxan (35 c.c.) were heated together at 100° for 16 hours. The dioxan was removed by distillation *in vacuo*, the residue dissolved in ether, and the ethereal solution washed with dilute sodium hydroxide solution and shaken with hydrochloric acid (125 c.c. of 2*N*.). The white solid (12 g.) which separated was collected and crystallised from water, giving **4-*morpholino*-1 : 1-*diphenylbut*-2-*yn*-1-*ol hydrochloride***, small prisms (from water), m. p. 203° (decomp.; bath preheated to 190°) (Found: C, 69·5; H, 6·0; N, 3·95. $C_{20}H_{21}O_2N,HCl$ requires C, 69·9; H, 6·4; N, 4·1%). The free *amine*, obtained by basification of a warm aqueous solution of the hydrochloride, formed colourless needles from methyl alcohol, m. p. 150—152° (Found: C, 78·4; H, 7·1; N, 4·8. $C_{20}H_{21}O_2N$ requires C, 78·2; H, 6·85; N, 4·6%). The *methiodide* formed plates, m. p. 168—170° (decomp.), from methyl alcohol (Found: C, 55·9; H, 5·45; N, 3·0. $C_{21}H_{24}O_2NI$ requires C, 56·1; H, 5·35; N, 3·1%). The acetyl derivative could not be prepared.

(b) *From diphenylethynylcarbinol.* The carbinol (21 g.), paraformaldehyde (4 g.), morpholine (10 g.), and dioxan (30 c.c.) were heated at 100° for 16 hours. The dioxan was removed by distillation

in vacuo, the residue dissolved in ether and extracted with hydrochloric acid (20 c.c. of concentrated acid in 150 c.c. of water), and the aqueous acid layer basified with 10*N*-sodium hydroxide. The gummy precipitate was extracted with ether, and, after drying ($MgSO_4$) and evaporation, crystallised from methanol to give 4-morpholino-1 : 1-diphenylbut-2-yn-1-ol (0·3 g., 1%) as needles, m. p. 150—152°, identical with those obtained under (a), above.

4-*Dimethylamino*-1 : 1-*diphenylpent*-2-*en*-1-*ol*.—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (5 g.), dissolved in methyl alcohol (100 c.c.), was hydrogenated at ordinary temperature and atmospheric pressure by using palladium on calcium carbonate as catalyst. After 40 minutes, absorption was complete (410 c.c.; calc. for H_2, 405 c.c.). After evaporation of the filtered solution *in vacuo*, the residue was recrystallised from light petroleum (b. p. 40—60°), giving 4-*dimethylamino*-1 : 1-*diphenylpent*-2-*en*-1-*ol* (4 g.) as colourless plates, m. p. 72—74° (Found : C, 81·0; H, 7·95; N, 4·9. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2; N, 5·0%). The *methiodide* formed colourless prisms, m. p. 229—230° (decomp.; bath preheated to 210°), from water (Found : C, 56·55; H, 6·1; N, 3·25. $C_{20}H_{26}ONI$ requires C, 56·7; H, 6·1; N, 3·3%).

4-*Dimethylamino*-1 : 1-*diphenylpentan*-1-*ol*.—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (5 g.), dissolved in methyl alcohol (100 c.c.), was hydrogenated at ordinary temperature and pressure by means of Raney nickel catalyst. The reduction proceeded in two stages, 415 c.c. (theory for H_2, 405 c.c.) being absorbed in one hour and 820 c.c. (theory for $2H_2$, 810 c.c.) in 12 hours, absorption then ceasing. Evaporation of the filtered solution *in vacuo* and crystallisation of the residue from light petroleum (b. p. 40—60°) gave 4-*dimethylamino*-1 : 1-*diphenylpentan*-1-*ol* (3·6 g.) as colourless prisms, m. p. 79—80° (Found : C, 80·7; H, 8·65; N, 5·4. $C_{19}H_{25}ON$ requires C, 80·5; H, 8·8; N, 4·95%). The *methiodide* formed colourless prisms, m. p. 237—238°, from methanol (Found : C, 56·4; H, 6·5; N, 3·05. $C_{20}H_{28}ONI$ requires C, 56·5; H, 6·6; N, 3·3%).

4-*Diethylamino*-1 : 1-*diphenylpent*-2-*en*-1-*ol*.—This was obtained by reduction of 4-diethylamino-1 : 1-diphenylpent-2-yn-1-ol as described above for the dimethylamino-analogue. The *base* (61% yield) formed colourless plates, m. p. 68—70°, from light petroleum (b. p. 40—60°) (Found : C, 81·2; H, 8·5; N, 4·2. $C_{21}H_{27}ON$ requires C, 81·5; H, 8·7; N, 4·5%). The *methiodide* formed colourless plates, m. p. 190—192° (decomp.), from methyl alcohol (Found : C, 58·25; H, 6·35; N, 2·95. $C_{22}H_{30}ONI$ requires C, 58·5; H, 6·7; N, 3·1%).

4-*Diethylamino*-1 : 1-*diphenylpentan*-1-*ol*.—4-Diethylamino-1 : 1-diphenylpent-2-yn-1-ol (7 g.) in methyl alcohol (100 c.c.) was hydrogenated at room temperature and pressure in presence of Raney nickel catalyst. Absorption of 510 c.c. (theory for H_2, 513 c.c.) took 15 minutes, and that of 1400 c.c. 11 hours, after which the experiment was stopped although absorption was still occurring. The solvent was distilled from the filtered solution, and the presence of diethylamine in the distillate was established by isolation of its hydrochloride and picrolonate, and by the formation of *N*-α-naphthyl-*N'N'*-diethylurea, identical with authentic specimens. The residue after removal of methyl alcohol was dissolved in ether and extracted with dilute hydrochloric acid, the aqueous acid extract basified with 10*N*-sodium hydroxide, and the precipitated amine isolated with ether. Crystallisation of the residue from light petroleum (b. p. 40—60°) gave 4-*diethylamino*-1 : 1-*diphenylpentan*-1-*ol* (3·0 g.) as colourless plates, m. p. 92—94° (Found : C, 81·05; H, 8·9; N, 4·25. $C_{21}H_{29}ON$ requires C, 81·0; H, 9·3; N, 4·5%). The *methiodide* formed prisms, m. p. 178—180° (decomp.), from aqueous methyl alcohol (Found : C, 53·9; H, 7·1; N, 3·25. $C_{22}H_{32}ONI,H_2O$ requires C, 56·05; H, 7·2; N, 2·9%). Attempts to carry out the complete reduction with platinum or with palladium under pressure gave low yields of product and much fission to diethylamine.

4-*Morpholino*-1 : 1-*diphenylpent*-2-*en*-1-*ol*.—4-Morpholino-1 : 1-diphenylpent-2-yn-1-ol (5 g.) was reduced with a palladium–calcium carbonate catalyst as described for the dimethylamino-analogue. The *base* (4·4 g.) formed colourless elongated prisms, m. p. 93—94°, from light petroleum (b. p. 60—80°) (Found : C, 77·6; H, 7·6; N, 4·35. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%). The *methiodide* formed colourless prisms, m. p. 232° (decomp.; bath preheated to 210°), from methyl alcohol (Found : C, 56·35; H, 5·8; N, 2·7. $C_{22}H_{28}O_2NI$ requires C, 56·7; H, 6·0; N, 3·0%). Attempts to effect the saturation of the acetylenic linkage by means of platinum oxide gave a 16% yield of the ethylenic amine, and much morpholine. Raney nickel or palladium–calcium carbonate with hydrogen under pressure also gave a low yield of the ethylenic amine, and much fission occurred. Attempted further hydrogenation of the ethylenic amine gave the unchanged base in low yield and decomposition products, and reduction with sodium and liquid ammonia was also unsuccessful.

4-*Morpholino*-1 : 1-*diphenylbut*-2-*en*-1-*ol*.—4-Morpholino-1 : 1-diphenylbut-2-yn-1-ol (3·2 g.) was hydrogenated in dioxan (100 c.c.) at room temperature and atmospheric pressure with palladised calcium carbonate as catalyst. The hydrogenation was stopped after an absorption of 280 c.c. (absorption was still proceeding rapidly; theory for H_2, 240 c.c.), and after filtration and evaporation *in vacuo* gave a product (3 g.), m. p. 50—70°, which after three recrystallisations from methyl alcohol and two from light petroleum (b. p. 60—80°) gave 4-*morpholino*-1 : 1-*diphenylbut*-2-*en*-1-*ol* (2 g.) as needles, m. p. 88—89° (Found : C, 77·7; H, 7·4; N, 4·3. $C_{20}H_{23}O_2N$ requires C, 77·8; H, 7·4; N, 4·5%). The *methiodide* formed small prisms, m. p. 203° (decomp.; bath preheated to 190°), from water (Found : C, 55·7; H, 5·8; N, 3·1. $C_{21}H_{26}O_2NI$ requires C, 55·9; H, 5·8; N, 3·1%).

4-*Morpholino*-1 : 1-*diphenylbutan*-1-*ol*.—Hydrogenation was carried out as described for the semi-hydrogenation but the experiment was continued until absorption was complete. The *base* was obtained in 83% yield as silky needles, m. p. 128—130°, from light petroleum (b. p. 60—80°) (Found : C, 76·9; H, 8·0; N, 4·55. $C_{20}H_{25}O_2N$ requires C, 77·2; H, 8·0; N, 4·5%). The *methiodide* formed plates, m. p. 204° (decomp.; bath preheated to 190°), from water (Found : C, 55·5; H, 5·95; N, 3·4. $C_{21}H_{28}O_2NI$ requires C, 55·6; H, 6·2; N, 3·1%).

4-*Dimethylamino*-1 : 1-*diphenylpent*-1-*en*-3-*one*.—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (5 g.) was heated with dilute sulphuric acid (20 c.c. of concentrated acid in 100 c.c. of water) at 100° for 30 minutes. After cooling, 10*N*-sodium hydroxide (70 c.c.) was added, and the solution, after filtration from sodium sulphate, was extracted with ether to remove non-basic by-products. The aqueous layer was basified with 10*N*-sodium hydroxide and extracted with ether, and the ether dried ($MgSO_4$) and

evaporated. The product crystallised from light petroleum (b. p. 40—60°) to give *4-dimethylamino-1 : 1-diphenylpent-1-en-3-one* as yellowish needles, m. p. 52—54° (2·9 g., 58%) (Found : C, 81·3; H, 7·55; N, 5·1. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5; N, 5·0%). The *methiodide* formed cream-coloured plates, m. p. 220° (decomp.; bath preheated to 205°), from methanol (Found : C, 57·5; H, 5·7; N, 3·5. $C_{20}H_{24}ONI$ requires C, 57·0; H, 5·7; N, 3·3%).

This amino-ketone was very unstable; purified specimens decomposed to a brown liquid in 72 hours, and impure specimens were even less stable. For this reason the complete preparation and the utilisation of the product were always carried out in one day. One of the products of decomposition was non-basic, and it was possible to recover some of the amino-ketone from a partly decomposed sample by extraction with acid.

3-Chloro-4-dimethylamino-1 : 1-diphenylpent-2-en-1-ol.—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (1 g.) was heated at 100° for 5 minutes with water (10 c.c.) and 10*N*-hydrochloric acid (5 c.c.). After cooling to 45°, the insoluble hydrochloride was collected and crystallised from alcohol, giving *3-chloro-4-dimethylamino-1 : 1-diphenylpent-2-en-1-ol hydrochloride* as white needles, m. p. 195° (decomp.) (0·5 g.) (Found : C, 63·25; H, 6·4. $C_{19}H_{20}ONCl,HCl,0·5H_2O$ requires C, 63·15; H, 6·7%). The free *base* formed white prisms, m. p. 56—58°, from light petroleum (b. p. 40—60°) (Found : C, 72·7; H, 6·85; N, 4·4; Cl, 11·8. $C_{19}H_{20}ONCl$ requires C, 72·3; H, 7·0; N, 4·4; Cl, 11·3%). The *methiodide* formed white prisms, m. p. 227° (decomp.; bath preheated to 210°), from alcohol (Found : C, 52·55; H, 5·55; N, 2·95. $C_{20}H_{23}ONClI$ requires C, 52·5; H, 5·5; N, 3·0%).

The use of very dilute hydrochloric acid in this reaction gave only unchanged amino-alcohol after 24 hours' boiling; concentrated hydrochloric acid (15 minutes at 100°), however, caused disruption of the molecule and gave a non-basic tar from which benzophenone was isolated as its dinitrophenylhydrazone (m. p. and mixed m. p. 232°).

3-Chloro-4-dimethylamino-1 : 1-diphenylpent-2-en-1-ol regenerates the original acetylenic amine on treatment with 5% methanolic potassium hydroxide at 80° for 1½ hours. On catalytic reduction with Raney nickel and hydrogen at room temperature and pressure, 20% of the material is recovered unchanged, the rest being converted into a non-basic resin. When the alcohol is heated with 30% sulphuric acid, 4-dimethylamino-1 : 1-diphenylpent-1-en-3-one is formed.

4-Diethylamino-1 : 1-diphenylpent-1-en-3-one.—4-Diethylamino-1 : 1-diphenylpent-2-yn-1-ol hydrochloride (3·3 g.), dissolved in water (50 c.c.), was boiled under reflux for 24 hours. After cooling, some oil was removed by ether-extraction, the aqueous layer was basified with dilute sodium hydroxide solution, and the product (a sticky solid) extracted with ether. After drying ($MgSO_4$) and evaporation, a viscous yellow oil was obtained, which on crystallisation from light petroleum gave only a low yield of recovered diethylaminodiphenylpentynol, m. p. 81—83°. Methylation of the crude oil with methyl iodide in acetone, however, gave pale yellow needles, m. p. 193°, from alcohol. This was not identical with the methiodide of the original amine, and is probably *4-diethylamino-1 : 1-diphenylpent-1-en-3-one methiodide* (Found : C, 58·5; H, 6·4; N, 3·6; I, 27·6. $C_{22}H_{26}ONI$ requires C, 58·6; H, 6·3; N, 3·1; I, 28·3%).

3-Chloro-4-morpholino-1 : 1-diphenylpent-2-en-1-ol.—4-Morpholino-1 : 1-diphenylpent-2-yn-1-ol (10 g.) was heated with hydrochloric acid (36%; 50 c.c.) and water (100 c.c.) at 80—90° for 5 minutes. After cooling to 40°, the precipitated hydrochloride (5 g., 41%) was collected and recrystallised from alcohol, giving *3-chloro-4-morpholino-1 : 1-diphenylpent-2-en-1-ol hydrochloride* as needles, m. p. 176° (decomp.) (Found : C, 63·55; H, 6·3; N, 3·3. $C_{21}H_{24}O_2NCl,HCl$ requires C, 63·9; H, 6·3; N, 3·6%). The free *base*, regenerated from the hydrochloride with sodium hydroxide, separated from methyl alcohol in small plates, m. p. 105—106° (Found : C, 70·4; H, 6·9; N, 4·0; Cl, 10·7. $C_{21}H_{24}O_2NCl$ requires C, 70·6; H, 6·7; N, 3·9; Cl, 10·1%). The *methiodide* formed minute needles, m. p. 198° (decomp.), from methyl alcohol (Found : C, 52·5; H, 5·4; N, 2·5. $C_{22}H_{27}O_2NClI$ requires C, 52·8; H, 5·4; N, 2·8%).

Treatment of the base with methanolic potassium hydroxide regenerated 4-morpholino-1 : 1-diphenylpent-2-yn-1-ol, m. p. and mixed m. p. 140—142°. Reduction with Raney nickel and hydrogen at room temperature and pressure gave 20% of recovered chloro-amine and much unidentified tar.

4-Morpholino-1 : 1-diphenylpent-1-en-3-one.—4-Morpholino-1 : 1-diphenylpent-2-yn-1-ol (2 g.) was dissolved in dilute sulphuric acid (8 c.c. of concentrated acid and 40 c.c. of water), and the solution heated on the steam-bath for 30 minutes. The cooled solution was made strongly alkaline with 10*N*-sodium hydroxide, and the precipitated oil extracted with ether. The ethereal solution was extracted with 2*N*-hydrochloric acid, and the acidic extract basified (10*N*-NaOH), and again extracted with ether. Evaporation of the ether gave a yellow oil which could not be induced to crystallise. Addition of dry hydrogen chloride in ether afforded the *hydrochloride*, m. p. 184—185°, as white needles from alcohol (Found : C, 70·3; H, 6·75; N, 3·9. $C_{21}H_{23}O_2N,HCl$ requires C, 70·5; H, 6·7; N, 3·9%), which depressed the m. p. (186°) of the hydrochloride of the starting material. Treatment of the crude oil with methyl iodide gave the *methiodide* as yellow prisms, m. p. 197° (decomp.), from alcohol (Found : C, 57·2; H, 6·0; N, 2·9. $C_{22}H_{26}O_2NI$ requires C, 57·0; H, 5·7; N, 3·0%). The methiodide depressed the m. p. (202—203°) of the (white) methiodide of the starting material. The same material, identified as the hydrochloride and methiodide, was formed when 3-chloro-4-morpholino-1 : 1-diphenylpent-2-en-1-ol (above) was treated at 100° for 3 hours with 35% sulphuric acid.

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75. *The Effect of Bond Structure on the Transformation of o-Aroyloxyacetoarones into o-Hydroxydiaroylmethanes. Baker–Venkataraman Transformation.*

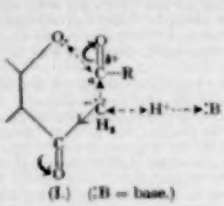
By N. V. Nowlan, P. A. Slavin, and T. S. Wheeler.

The experimental results indicate that the Baker–Venkataraman transformation of *o*-aroyloxyacetoarones into *o*-hydroxydiaroylmethanes takes place more rapidly across the 2 : 3-bond (single bond) in naphthalene than across the 1 : 2-bond (double bond). This is attributed to ester-type neutralisation across the double bond, and is in accordance with the view (Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291) that the transformation involves a base-catalysed intramolecular Claisen condensation. Preliminary results with *o*-aroyloxyacetylindanes do not seem to be in accord with the Mills–Nixon view of bond distribution in indane.

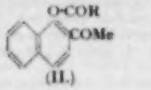
The tendency of *o*-hydroxydiaroylmethanes, HO CO·CH$_2$·CO·R, to undergo spontaneous cyclisation to the corresponding flavones when R contains an electrophilic (nitro-) group is discussed. A number of new 4-pyrones are described.

It has not been found possible to transform *o*-arylsulphonyloxyacetophenones.

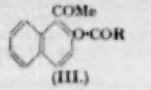
The transformation of *o*-aroyloxyacetoarones into *o*-hydroxydiaroylmethanes (Baker, *J.*, 1933, 1381; Mahal and Venkataraman, *J.*, 1934, 1767) has been shown by Doyle *et al.* (*Proc. Roy. Dublin Soc.*, 1948, **24**, 291) to be a base-catalysed intramolecular Claisen condensation involving a nucleophilic displacement of oxygen on carbon as indicated by the transition compound (I). This paper describes an investigation of this transformation across the $C_{(1)}$–$C_{(2)}$ and $C_{(2)}$–$C_{(3)}$ bonds of naphthalene, which have as regards the chemical reactivity of naphthalene compounds the quality, respectively, of double and single bonds [cf. Fieser, "Organic Chemistry" (Gilman), 1943, Vol. I, 145]. The experimental work was concerned mainly with the base-catalysed transformation of *o*-(nitrobenzoyloxy)acetonaphthones (II, III, and IV;



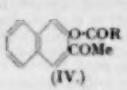
(I.) (:B = base.)



(II.)



(III.)



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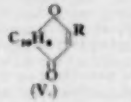

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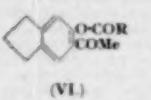
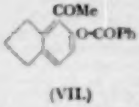


(VI.)



(VII.)

R = *o*-, *m*-, or *p*-nitro- or 3 : 5-dinitro-phenyl) into the corresponding *o*-hydroxy-diketones, $C_{10}H_6(OH)$·CO·CH_2·CO·R, which in some instances cyclised spontaneously to form the benzflavone (V). The transformation of other 2-acyloxy-3-acetonaphthones (IV; R = Me, Ph, styryl, or 2-methoxy-3-naphthyl), and of some esters of *o*-hydroxyacetylindanes (VI; R = Me, Ph, and *p*-nitrophenyl) and (VII), was also investigated. Attempts to transform benzene- and toluene-sulphonic esters of the *o*-hydroxyacetonaphthones (see Table III) using a variety of basic catalysts (see Doyle *et al.*, *loc. cit.*) were unsuccessful: the sulphonyl group, though electrophilic, is less so than the carbonyl group (Kohler and Potter, *J. Amer. Chem. Soc.*, 1935, **57**, 1316; Connor *et al.*, *ibid.*, 1936, **58**, 1386). When 2-benzenesulphonyloxy-3-acetonaphthone was treated with triphenylmethylsodium, a compound giving analytical figures corresponding to $C_{44}H_{34}O_5S$ [? 2 : 3-$C_{10}H_4$(COMe)·O·SPh$(CPh_3)_2$] was obtained. Transformation of the sulphonic esters was also attempted using boron trifluoride as an acid catalyst (see Breslow and Hauser, *J. Amer. Chem. Soc.*, 1940, **62**, 2385) but without success.

Results with o-Acyloxyacetonaphthones.—The trend of the results obtained with the nitro-esters summarised in Table I, while not conclusive, indicates that generally transformation takes place across the $C_{(2)}$–$C_{(3)}$ single-type bond more rapidly than across the $C_{(1)}$–$C_{(2)}$ double-type bond. Comparative experiments with 2-benzoyloxy-1-acetonaphthone (III; R = Ph) (Bhalla *et al.*, *J.*, 1935, 870) and *2-benzoyloxy-3-acetonaphthone* (IV; R = Ph) gave, similarly, more rapid transformation with the latter compound. Smooth and rapid transformation was also obtained with *2-cinnamoyloxy-3-acetonaphthone* (IV; R = styryl) and *2-(2-methoxy-3-naphthoyloxy)-3-acetonaphthone* (IV; R = 2-methoxy-3-naphthyl). It was not found possible to transform 2-acetoxy-3-acetonaphthone (IV; R = Me) (Fries and Schimmelschmidt, *Ber.*,

TABLE I.

Results with nitrobenzoyloxyacetonaphthones.

(II, III, and IV; R = *o*-, *m*-, or *p*-nitro- or 3 : 5-dinitro-phenyl.)

	Acetonaphthone.					
	1-Hydroxy-2-acetonaphthone (II).		2-Hydroxy-1-acetonaphthone (III).		2-Hydroxy-3-acetonaphthone (IV).	
Aroyl radical.	Reaction time, mins.	Yield,[1] %	Reaction time, mins.	Yield,[1] %	Reaction time, mins.	Yield,[1] %
2-Nitrobenzoyl-	2	26 D	6	2 DF	2	30 DF
3-Nitrobenzoyl-	7	22 D	8	21 F	1	30 D
4-Nitrobenzoyl-	5	58 D	7	28 D	<1	46 D
3 : 5-Dinitrobenzoyl-	3	Tar	6	50 F[2]	1	3 F

These transformations were carried out under controlled conditions in boiling pyridine with potassium hydroxide as base. For details see the Experimental section. Potassium hydroxide was chosen after a number of the bases used by Doyle *et al.* (*loc. cit.*) had been tested.

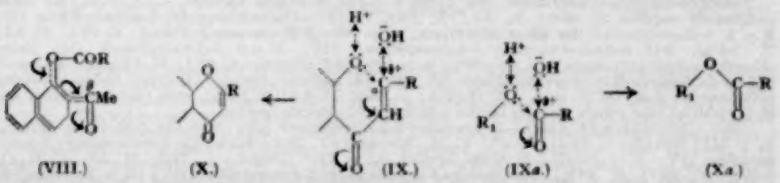
[1] Yields are calculated on the aroyloxyacetonaphthone. D indicates yield of diketone; F shows yield of flavone when produced by spontaneous cyclization of diketone; DF gives yield of flavone obtained by cyclization of material (crude diketone) which could not readily be purified.

[2] 3′ : 5′-*Dinitro*-3-(3 : 5-*dinitrobenzoyl*)-5 : 6-*benzflavone* was the probable product of the transformation.

1925, **58**, 2835). *o*-Acetoxyacetoarones (I; R = Me) are difficult to transform (cf. **Baker**, *loc. cit.*; Virkar and Wheeler *J.*, **1939**, 1679; Geissman, *J. Amer. Chem. Soc.*, **1949**, **71**, 1498) as the anionoid effect of the methyl group reduces the electrophilic nature of $C_{(a)}$ (I). Gowan (private communication) has, however, succeeded in transforming *o*-acetoxyacetophenone into *o*-hydroxybenzoylacetone using triphenylmethylsodium as the basic catalyst.

These results support the view of Doyle *et al.* (*loc. cit.*) as to the mechanism of the transformation. The mobile π electrons of the $C_{(1)}$–$C_{(2)}$ bond facilitate ester-type neutralisation of the carbonyl carbon $C_{(a)}$ (VIII); such neutralisation occurs less readily across the $C_{(2)}$–$C_{(3)}$ bond in which the density of electrons is low (see Pullman, *Ann. Chim.*, **1947**, **2**, 5). The occurrence of such neutralisation across the $C_{(1)}$–$C_{(2)}$ bond is shown by the exceptionally high basic strength of 2-nitro-3-naphthylamine as compared with 2-nitro-1-naphthylamine and 1-nitro-2-naphthylamine (cf. Bryson, *Trans. Faraday Soc.*, **1949**, **45**, 257; Hodgson and Turner, *J.*, **1943**, 635). The argument is supported by the non-existence of 2 : 3-naphthaquinone; an *o*-quinonoid form is involved in the type of neutralisation shown in (VIII) (see Waters, *J.*, **1948**, 727).

Preliminary Results with o-*Aroyloxyacetylindanes.*—*5-Benzoyloxy-6-acetylindane* (VI; R = Ph) was found in comparative experiments to be transformed into the corresponding *diketone* more rapidly than was *5-benzoyloxy-4-acetylindane* (VII). This result is unexpected if the Mills–Nixon structure (*J.*, 1930, 2510), which is shown in (VI) and (VII), is assumed for indane.



However, though Baker's well-known investigation on chelation effects (*J.*, 1937, 476) supports this structure for *o*-hydroxyacetylindanes, the results of extensive work on the reactivity of indane and of its derivatives indicate that, if bond fixation is present, it is not so well-defined as in the naphthalene series, but is more sensitive to the substituents present and to the reagents employed [see Fieser, *op. cit.*, p. 139; Hippchen, "On the arrangement of the double bonds in hydrindene (indane)," F.I.A.T. Final Report, No. 1033 (1947); "Elsevier's Encyclopædia of Organic Chemistry," **1948**, **12**, *A*, 103; Springall *et al.*, *J.*, **1949**, 1524]. It is hoped to investigate further the transformation of esters of the type shown in (VI) and (VII). 5-Acetoxy-6-acetylindane (VI; R = Me) (Baker, *loc. cit.*) could not be transformed.

Flavone Formation.—It will be seen from Table I that three of the nitro-diketones (indicated

by F) cyclised, when formed, to the flavone (cf. Doyle *et al.*, *loc. cit.*). This cyclisation is of course analogous to esterification (IX; IXa; X; Xa); it involves a nucleophilic displacement of hydroxyl on carbon (see Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686) and is therefore promoted by the presence, in R, of an electrophilic (nitro-) group, which increases the cationoid activity of C_{α} (IX). It will be noted that 2-(3 : 5-*dinitrobenzoyloxy*)-1-*acetonaphthone* (III; R = 3 : 5-dinitrophenyl) yielded directly a compound giving analytical figures corresponding to the related 3-aroylated *flavone* (Table I, footnote 2).

Experimental.

Preparation of o-Hydroxyacetoarones and their Esters.—1-Hydroxy-2-acetonaphthone (Witt and Braun, *Ber.*, 1914, **47**, 3216), 2-hydroxy-1-acetonaphthone (Fries, *Ber.*, 1921, **54**, 709), 2-hydroxy-3-acetonaphthone (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2835), 5-hydroxy-6-acetylindane, and 5-hydroxy-4-acetylindane (Baker, *J.*, 1937, 476) were synthesised as described by the authors cited. In this preparation of 1-hydroxy-2-acetonaphthone it was found essential to keep the temperature of the reaction mixture below 140°, otherwise 1-hydroxy-2 : 4-diacetylnaphthalene was produced.

The esters were prepared by the pyridine–acid chloride method (cf. Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291); the yields were usually over 60%. Completion of esterification was determined by extracting an acidified sample of the reaction mixture with chloroform, diluting the extract with alcohol, and testing for free *o*-hydroxy-diketone with alcoholic ferric chloride. Serial numbers have been assigned to the carboxylic esters to facilitate cross-reference.

Those of the sulphonic esters which did not solidify rapidly when the reaction mixture was acidified were extracted with chloroform, and the extracts were washed with aqueous sodium carbonate and with water and dried (Na_2SO_4). The residue obtained on removal of the solvent was distilled at about 10^{-2} mm. before recrystallisation.

Mononitrobenzoylarylacetonaphthones.—These compounds (see Tables I and II) were colourless to yellow, excepting No. 4 which was red.

Table II.

γ-(*x*-*Nitrobenzoyloxy*)-*z*-*acetonaphthones.*

(II, III, and IV; R = *o*-, *m*-, and *p*-nitrophenyl) ($C_{18}H_{11}O_4N$ requires C, 68·1; H, 3·9; N, 4·2%).

	Ester.					Found, %.		
Serial no.	*x*.	*y*.	*z*.	M. p.	Crystallizing solvent.	C.	H.	N.
1	2′	1	2	115—116°	Alcohol–dioxan	68·0	4·1	4·3 [1]
2	3′	1	2	151—152	Alcohol	—	—	4·4 [2]
3	4′	1	2	150—151	Alcohol–dioxan	68·3	3·9	4·3 [2]
4	2′	2	1	146—148	Acetone–aqueous alcohol	67·3	3·9	4·3 [1]
5	3′	2	1	174—176	Chloroform	68·1	3·9	4·5 [1]
6	4′	2	1	137—138	Acetone–aqueous alcohol	67·3	3·9	4·2 [1]
7	2′	2	3	165	Alcohol–dioxan	68·2	4·1	4·2 [1]
8	3′	2	3	146—148	Alcohol–dioxan	67·8	3·9	4·0 [1]
9	4′	2	3	177—179	Alcohol–dioxan	67·7	3·9	4·0 [1]

[1] New compound. [2] Virkar, *J. Univ. Bombay*, 1942, **11**, 136.

Dinitrobenzoylarylacetonaphthones (see Table I).—The molecular formula, $C_{19}H_{12}O_7N_2$, for these compounds requires C, 60·0; H, 3·1; N, 7·4%. 1-(3 : 5-*Dinitrobenzoyloxy*)-2-*acetonaphthone* (II; R = 3 : 5-dinitrophenyl) (10) (from chloroform), m. p. 209—212° (decomp.) (Found: C, 59·7; H, 3·3; N, 7·4%), 2-(3 : 5-*dinitrobenzoyloxy*)-1-*acetonaphthone* (III; R = 3 : 5-dinitrophenyl) (11) (from chloroform–light petroleum (b. p. 60—80°)), m. p. 200—202° (Found: C, 60·2; H, 3·2; N, 7·8%), and 2-(3 : 5-*dinitrobenzoyloxy*)-3-*acetonaphthone* (IV; R = 3 : 5-dinitrophenyl) (12) (from chloroform–light petroleum (b. p. 40—60°)), m. p. 173° (Found: C, 59·9; H, 3·2; N, 7·3%), were readily obtained (*ca.* 80% yield) as pale yellow crystals by the pyridine–acid chloride method.

Other Carboxylic Acid Esters.—2-*Benzoyloxy*-3-*acetonaphthone* (IV; R = Ph) (13) (from ligroin), m. p. 111° (Found: C, 78·5; H, 4·7. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·8%), 2-*cinnamoyloxy*-3-*acetonaphthone* (IV; R = styryl) (14) (from ligroin), m. p. 121° (Found: C, 79·6; H, 5·2. $C_{21}H_{16}O_3$ requires C, 79·7; H, 5·1%), 2-(2-*methoxy*-3-*naphthoyloxy*)-3-*acetonaphthone* (IV; R = 2-methoxy-3-naphthyl) (15) (from benzene and alcohol), m. p. 191° (Found: C, 77·7; H, 5·0. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%), 5-*benzoyloxy*-6-*acetylindane* (VI; R = Ph) (16) (from aqueous alcohol), m. p. 87—88° (Found: C, 77·0; H, 5·9. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%), 5-(*p*-*nitrobenzoyloxy*)-6-*acetylindane* (VI; R = *p*-nitrophenyl) (17) (from aqueous alcohol), m. p. 104—105° (Found: C, 66·6; H, 4·8; N, 4·3. $C_{18}H_{15}O_5N$ requires C, 66·5; H, 4·6; N, 4·3%), and 5-*benzoyloxy*-4-*acetylindane* (VII) (18) (from aqueous methyl alcohol and ligroin), m. p. 89—90° (Found: C, 77·1; H, 5·6. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%), were obtained as colourless crystals.

Sulphonic Acid Esters.—Results for these compounds, all colourless, are given in Table III.

Action of Triphenylmethylsodium on 2-Benzenesulphonyloxy-3-acetonaphthone.—2-Benzenesulphonyloxy-3-acetonaphthone (0·5 g.) contained in a reaction flask filled with nitrogen was treated with an ethereal solution of triphenylmethylsodium, prepared, stored, and delivered into the reaction flask in an atmosphere of nitrogen using the procedure of Hauser and Hudson ("Organic Reactions," 1942, Vol. I, 286). Addition of the reagent was discontinued when the red colour of its solution was no longer discharged. The mixture was shaken for 1 hour and treated with water. The insoluble *product* (0·5 g.)

separated from chloroform and from glacial acetic acid in colourless crystals, m. p. 184°, insoluble in aqueous alkali, acetone, and ether, soluble in chloroform, and unaffected by hot hydrobromic acid in glacial acetic acid (Found: C, 86·5, 86·4, 86·3, 86·3; H, 5·8, 5·9, 5·5, 5·6; S, 4·4, 4·7. $C_{16}H_{16}O_3S$ requires C, 86·2; H, 5·6; S, 4·1%).

TABLE III.

Sulphonic acid esters, x-R-*sulphonyloxy*-y-*acetonaphthones.*[1]

(*A*; R = benzene: $C_{18}H_{14}O_5S$ requires C, 66·3; H, 4·3; S, 9·8%.
B; R = toluene: $C_{19}H_{16}O_5S$ requires C, 67·1; H, 4·7; S, 9·4%.)

	Ester.				Found, %		
R.	x.	y.	M. p.	Crystallizing solvent.	C.	H.	S.
A; Benzene	2	1	72—74°	Aqueous alcohol	66·2	4·4	9·6
"	2	3	84—86	Alcohol	66·1	4·3	9·4
B; *o*-Toluene	1	2	63—65	Alcohol	66·9	4·9	9·5
"	2	1	60—62	Light petroleum (b. p. 60—80°)	67·0	4·8	9·4
"	2	3	110—112	Alcohol	67·0	4·8	9·0
p-Toluene	1	2	99—101	Aqueous alcohol	66·9	4·7	9·6
"	2	1	98—99	Alcohol	67·3	4·9	9·3
"	2	3	84—86	Alcohol	66·8	4·7	9·0

[1] These compounds are new.

Preparation of 1 : 3-*Diketones.—Transformation into ketones of the nitro-esters listed in Table II.* Potassium hydroxide (*ca.* 0·1 g.) was crushed between warm dry filter-papers and rapidly transferred to a boiling pyridine solution (5 ml.) of the ester (0·5 g.) to be transformed. Heating under reflux was continued until the solution, at first red, became brown, and solid separated. The mixture was cooled, diluted with water (20 ml.), and filtered. The filtrate was brought to pH 6 (glass electrode) with glacial acetic acid (*ca.* 0·4 ml.), and after an hour the precipitated diketone was collected and crystallised or, if difficult to purify, cyclised to the flavone. The presence of a nitro-group, particularly in the *ortho*-position, promotes the formation of resin and, if heating was continued until the solution became black, an unworkable product was obtained. Acidification beyond pH 6 caused precipitation of resin. Results for the nitrobenzoyl-o-hydroxynaphthoylmethanes prepared in this way are given in Table IV. The colour of these compounds varied from yellow to orange.

TABLE IV.

x-*Nitrobenzoyl*-y-*hydroxy*-z-*naphthoylmethanes.*

($C_{19}H_{11}O_5N$ requires C, 68·1; H, 3·9; N, 4·2%.)

Corresponding ester	Diketone.					Found, %		
no. of Table II.	x.	y.	z.	M. p.	Crystallizing solvent.	C.	H.	N.
1	2	1′	2′	173—175°	Aqueous acetone	67·6	4·1	4·1 [1]
2	3	1′	2′	191	Acetone	68·4	3·9	4·2 [2]
3	4	1′	2′	222—224	Tetrahydrofurfuryl alcohol	67·5	4·0	4·2 [2]
6	4	2′	1′	168—170	Alcohol	67·9	4·0	4·2 [1]
8	3	2′	3′	182—183	Acetone	67·7	3·9	4·5 [1]
9	4	2′	3′	228—230	Acetone	68·1	4·2	4·2 [1]

[1] New compound. [2] Virkar, *loc. cit.*

Transformation of other esters of o-*hydroxyacetonaphthones. Benzoyl*-2-*hydroxy*-3-*naphthoylmethane.* A solution of 2-benzoyloxy-3-acetonaphthone (IV; R = Ph) (ester no. 13) (1·2 g.) in pyridine (5 ml.) was treated with alcoholic sodium ethoxide (3 ml. of a solution containing 1 g. of sodium in 25 ml. of alcohol). The sodium salt of the diketone separated rapidly. The mixture was diluted with water and acidified with 10% hydrochloric acid. The solid (1·0 g.) thus obtained crystallised from aqueous alcohol in yellow needles, m. p. 129—130° (Found: C, 78·4; H, 4·8. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·8%). In comparative experiments (ester, 45 mg.; pyridine, 1 ml.; sodium ethoxide, 0·5 ml. of the solution referred to above) 2-benzoyloxy-1-acetonaphthone (Ullal, Shah, and Wheeler, *J.*, 1940, 1499) showed a slower rate of transformation. No effect was apparent until 30 minutes after addition of the base, as compared with the immediate precipitate obtained with the 2 : 3-compound.

Cinnamoyl-2-*hydroxy*-3-*naphthoylmethane* (from glacial acetic acid), m. p. 160° (Found: C, 79·3; H, 4·9. $C_{21}H_{16}O_3$ requires C, 79·7; H, 5·1%), and 2-*hydroxy*-2′-*methoxy*-3 : 3′-*dinaphthoylmethane* (from glacial acetic acid), m. p. 181—182° (Found: C, 77·1; H, 5·0. $C_{32}H_{24}O_5$ requires C, 77·8; H, 4·9%), were prepared as yellow crystals from the corresponding esters (nos. 14 and 15 respectively). As with 2-benzoyloxy-3-acetonaphthone (see above) the transformations were immediate.

Transformation of esters of o-*hydroxyacetylindanes. 5-Hydroxy*-6-*benzoylacetylindane.* A solution of 5-benzoyloxy-6-acetylindane (VI; R = Ph) (ester No. 16) (0·5 g.) in pyridine (5 ml.) was treated with solid potassium hydroxide (0·15 g.) previously crushed in a hot mortar, and the mixture was kept overnight. The yellow solid (0·47 g.) obtained when the reaction product was mixed with excess of 10% hydrochloric acid separated from aqueous alcohol in yellow needles, m. p. 99—101° (Found: C, 77·1; H, 5·8. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%). *5-Hydroxy*-6-*p-nitrobenzoylacetylindane* (from

aqueous dioxan), m. p. 225—227° (Found: C, 66·1; H, 4·5; N, 4·3. $C_{19}H_{15}O_4N$ requires C, 66·5; H, 4·6; N, 4·3%), and *5-hydroxy-4-benzoylacetylindane* (from aqueous alcohol), m. p. 114—115° (Found: C, 77·2; H, 5·6. $C_{18}H_{16}O_2$ requires C, 77·1; H, 5·7%), were similarly prepared as yellow crystalline solids from the corresponding esters (nos. 17 and 18). The yields were respectively 75 and 85%.

Comparative experiments were made on the rates of transformation of 5-benzoyloxy-6-acetylindane (VI; R = Ph) and 5-benzoyloxy-4-acetylindane (VII) using solid potassium hydroxide in pyridine as described above. With 5-benzoyloxy-6-acetylindane there was an immediate colour change and separation of the salt of the diketone was complete in 30 minutes. With the 5 : 4-isomer, 30 minutes elapsed before separation of the diketone salt commenced, and complete reaction required some hours.

Preparation of 4-Pyrones.—These compounds (flavones; benzchromones; indanopyrones) were obtained from esters, through diketones, by the following three methods:

A. The diketone was boiled with glacial acetic acid containing a few drops of concentrated hydrochloric acid, and the pyrone formed was separated by addition of hot water until a permanent opalescence was produced. The liquid was then slowly cooled (see Doyle *et al.*, *loc. cit.*). The yields were usually quantitative.

B. The crude product (diketone) of the transformation which could not readily be purified was cyclised by Method A.

C. The flavone resulted directly by spontaneous cyclisation of the diketone formed in the transformation reaction.

Mononitrobenzoflavones. Table V summarises results for the mononitrobenzoflavones obtained from the esters listed in Table II.

TABLE V.

x-*Nitro*-y : z-*benzflavones*.

($C_{19}H_{11}O_4N$ requires C, 71·9; H, 3·5; N, 4·4%.)

Corresponding ester no. in Table II.	Nitrobenzflavone. x.	y.	z.	M. p.	Found, %. C.	H.	N.	Method of preparation of flavone.
1	2′	7	8	222—224°	71·7	3·9	4·1	A [1]
2	3′	7	8	258	71·7	3·5	—	A [2]
3	4′	7	8	296	72·2	3·7	4·2	A [2]
4	2′	5	6	214—215	71·5	3·8	4·4	B [1]
5	3′	5	6	256—257	72·3	3·9	4·4	C [1]
6	4′	5	6	282—284	71·4	3·6	4·3	A [1]
7	2′	6	7	192—194	71·7	3·2	4·6	B [1]
8	3′	6	7	248—250	72·0	3·7	4·8	A [1]
9	4′	6	7	264	71·7	3·7	4·5	A [1]

These compounds, No. 1 excepted, were crystallised from glacial acetic acid; for No. 1 acetone–alcohol was used. They separated from the solvent in colourless to pale yellow crystals.

[1] *New compound.* [2] Virkar, *loc. cit.*

Dinitrobenzflavones. 3′ : 5′-*Dinitro*-3-(3 : 5-*dinitrobenzoyl*)-5 : 6-*benzflavone* (from glacial acetic acid and tetrahydrofurfuryl alcohol), m. p. 267—269° (Found: C, 56·8; H, 2·5; N, 10·0. $C_{31}H_{15}O_{11}N_5$ requires C, 56·1; H, 2·2; N, 10·1%), was obtained directly (method C) as a red powder in the transformation of 2-(3 : 5-dinitrobenzoyloxy)-1-acetonaphthone (III; R = 3 : 5-dinitrophenyl) (ester no. 11). 3′ : 5′-*Dinitro*-6 : 7-*benzflavone* (from dioxan), m. p. 330° (decomp.) (Found: C, 62·5; H, 2·9; N, 7·6. $C_{19}H_{10}O_8N_2$ requires C, 63·0; H, 2·8; N, 7·7%), was similarly obtained as a yellow powder from 2-(3 : 5-dinitrobenzoyloxy)-3-acetonaphthone (IV; R = 3 : 5-dinitrophenyl) (ester no. 12).

Other pyrones. The following 4-pyrones were prepared from the corresponding diketones using method A. The number of the ester corresponding to the diketone is given in brackets. 6 : 7-Benzflavone (linear naphthaflavone) (13) (colourless; from benzene–ligroin), m. p. 173° (Virkar and Wheeler, *J.*, 1939, 1682, give 171—172°) (Found: C, 83·3; H, 4·5. Calc. for $C_{19}H_{12}O_2$: C, 83·8; H, 4·4%); 2-*styryl*-6 : 7-*benzchromone* (14) (pale yellow; from benzene–ligroin), m. p. 168° (Found: C, 84·2; H, 4·9. $C_{21}H_{14}O_2$ requires C, 84·6; H, 4·7%); 2-(2-*methoxy*-3-*naphthyl*)-6 : 7-*benzchromone* (15) (pale yellow; from benzene–ligroin), m. p. 214° (Found: C, 81·3; H, 3·5. $C_{24}H_{16}O_3$ requires C, 81·8; H, 4·5%); 6-*phenylindano*(5′ : 6′-2 : 3)-4-*pyrone* (16) (colourless; from aqueous acetic acid), m. p. 161—162° (Found: C, 82·3; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%); 6-(p-*nitrophenyl*)*indano*(5′ : 6′-2 : 3)-4-*pyrone* (17) (yellow; from aqueous acetic acid), m. p. 265—267° (Found: C, 70·3; H, 4·3; N, 4·7. $C_{18}H_{11}O_4N$ requires C, 70·4; H, 4·2; N, 4·6%).

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76. *Some Physico-chemical Properties of Acridine Antimalarials, with Reference to their Biological Action. Part I. Basic Dissociation Constants and Reduction Potentials.*

By D. Ll. Hammick and S. F. Mason.

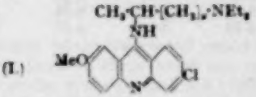
Two homologous series of acridine antimalarials analogous to Mepacrine (I) have been examined with the polarograph over a range of concentrations and pH values in order to measure reduction potentials and other quantities defining the oxidation–reduction behaviour of these compounds. Further measurements have been made of the pH values of aqueous and aqueous-alcoholic solutions of the dihydrochlorides of these derivatives in the presence of various amounts of alkali, and from the results obtained the basic dissociation constants of the compounds have been calculated. No definite correlation between antimalarial activity and either basicity or reduction potential has been observed.

Chemotherapeutic agents belonging to the same structural type appear to act on a given organism by the same or very similar mechanisms. The efficacy of their action varies widely however, and in some cases seems to depend on the values of certain physico-chemical properties, as Bell and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 2905) have discovered for the sulphonamides, and Albert and his co-workers (*Brit. J. Exp. Path.*, 1945, **26**, 160) for the simple aminoacridines.

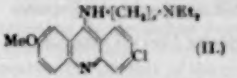
In the present work an attempt has been made to correlate the values of some physico-chemical properties of acridine antimalarials with their relative biological activities. The properties thought possibly relevant were selected by considering the nature of the action of Mepacrine on enzyme systems, bacteria, and the malaria parasite. Amongst other things, Mepacrine (I) interferes with the growth of bacteria by competing with natural bases, notably polyamines (Silverman and Evans, *J. Biol. Chem.*, 1944, **154**, 521), and also with the hydrogen carrier, riboflavin (Madinaveitia, *Biochem. J.*, 1946, **40**, 373; Haas, *J. Biol. Chem.*, 1944, **155**, 321). The competition of two bases and two oxidation–reduction systems for a common substrate may be said to be governed physico-chemically by the relative basicities and reduction potentials of the two substances. Thus it was thought that the relative values of the dissociation constants and the half-wave potentials of a structurally similar series of acridine antimalarials might possibly be related to their relative antimalarial activities.

Experimental.

Preparation of Materials.—Two homologous series of acridine antimalarials were prepared by standard methods (Magidson *et al.*, *Ber.*, 1936, **69**, 396; Breslow, *J. Amer. Chem. Soc.*, 1941, **63**, 156; 1946, **68**, 100). One, homologous with Mepacrine (I; $x = 3$), consisted of four members (I) having $x = 1$ to 4; the other possessed straight side-chains, six compounds (II) being prepared having $x = 2$ to 7.



(I.)



(II.)

2-Chloro-5-(1-diethylamino-2-propylamino)- (cf. I; $x = 1$), m. p. 223° (Found: C, 56·6; H, 6·4; N, 9·3; Cl, 22·4. $C_{21}H_{28}ON_4Cl_2,2HCl,H_2O$ requires C, 56·45; H, 6·7; N, 9·4; Cl, 23·05%), and *2-chloro-5-(7-diethylaminoheptylamino)-7-methoxyacridine dihydrochloride* (cf. II; $x = 7$), m. p. 240—242° (Found: C, 58·4; H, 7·2; N, 8·3; Cl, 21·0. $C_{31}H_{44}ON_4Cl_2,2HCl$ requires C, 58·3; H, 7·5; N, 8·8; Cl, 22·1%), 5-(3-diethylaminopropylamino)acridine dihydrochloride, m. p. 230—232° (cf. Gupta, *J. Indian Chem. Soc.*, 1945, **22**, 364, who give m. p. 230°), and the compounds listed in Table I were examined.

Table I.

2-Chloro-5-(R)-7-methoxyacridine dihydrochlorides (cf. I and II).

R.	M. p.	Literature.
4-Diethylamino-2-butylamino *	262°	Magidson, *loc. cit.*; m. p. 265°.
6-Diethylamino-2-hexylamino	112	Kritchewski, *J. Microbiol. U.S.S.R.*, 1935, **14**, 642; m. p. 114°.
2-Diethylaminoethylamino	258—259	Breslow, *loc. cit.*; m. p. 257—259°.
3-Diethylaminopropylamino	249—251	,, ,, m. p. 254—255°.
4-Diethylaminobutylamino †	246—249	Magidson, *loc. cit.*; m. p. 246—248°.
5-Diethylaminoamylamino	266—268	Breslow, ,, m. p. 266—267°.
6-Diethylaminohexylamino	250—253	,, ,, m. p. 253—255°

* Free base, m. p. 80°. † Hydrate.

Polarography.—The above compounds were examined polarographically over a range of concentrations in supporting electrolytes buffered to various pH values. The buffers were 0·05M. and were prepared after Sörensen: pH 2 and pH 4, citrate–hydrochloric acid; pH 5·5 and pH 7·3, phosphate; pH 9, glycine–sodium hydroxide.

Breyer, Buchanan, and Duewell (*J.*, 1944, 360) found that 5-aminoacridine is reduced in two steps of approximately equal height at the dropping-mercury electrode. We find similar steps with our acridines, all of which are derivatives of 5-aminoacridine. The half-wave potentials and diffusion currents of the four Mepacrine homologues (I), at a concentration of 10^{-4}M. in various buffered supporting electrolytes, are given in Table II. The half-wave potentials of the homologues of the straight-chain series (II) vary in a similar manner, and their values for a drug concentration of 10^{-4}M. in supporting electrolytes of pH 7·3 are given in Table III.

TABLE II.

Mepacrine Homologues (I).

The diffusion currents were measured in microamps., and the half-wave potentials in volts. All the potentials are negative, and were measured relative to the saturated calomel electrode.

		pH 2.		pH 4.		pH 5·5.		pH 7·3.		pH 9.	
		1st step.	2nd step.	1st step.	2nd step.	1st step.	2nd step.	1st step.	2nd step.	1st step.	2nd step.
$x = 1$	$E_{\frac{1}{2}}$	0·74	—	0·78	1·18	0·84	1·20	0·86	1·21	0·85	1·09
	I_d	0·26	—	0·26	0·26	0·20	0·16	0·16	0·11	0·04	0·04
$x = 2$	$E_{\frac{1}{2}}$	0·74	—	0·80	1·18	0·91	1·20	0·94	1·21	0·93	1·09
	I_d	0·23	—	0·22	0·22	0·21	0·19	0·19	0·18	0·19	0·20
$x = 3$	$E_{\frac{1}{2}}$	0·74	—	0·80	1·18	0·93	1·20	0·97	1·21	0·94	1·09
	I_d	0·23	—	0·22	0·20	0·20	0·12	0·18	0·11	0·18	0·12
$x = 4$	$E_{\frac{1}{2}}$	0·74	—	0·80	1·18	0·93	1·20	0·97	1·21	0·94	1·09
	I_d	0·21	—	0·19	0·15	0·19	0·13	0·18	0·12	0·16	0·12

At pH 2 the hydrogen discharge wave overlaps the second reduction steps of these acridines in all cases.

TABLE III.

2-Chloro-5-R-7-methoxyacridines (II).

R.	50% EtOH–H_2O. pK_{a_1}.	50% EtOH–H_2O. pK_{a_2}.	H_2O. pK_{a_1}.	$E_{\frac{1}{2}}$. 1st step.	$E_{\frac{1}{2}}$. 2nd step.
$Et_2N{\cdot}CH_2{\cdot}CHMe{-}$	6·51	8·32	7·31	0·86	1·21
$Et_2N{\cdot}[CH_2]_2{\cdot}CHMe{-}$	5·90	7·65	6·80	0·94	1·21
$Et_2N{\cdot}[CH_2]_3{\cdot}CHMe{-}$	5·11	7·13	6·47	0·97	1·21
$Et_2N{\cdot}[CH_2]_4{\cdot}CHMe{-}$	4·52	6·99	6·26	0·97	1·21
$Et_2N{\cdot}[CH_2]_2{-}$	6·01	7·84	6·95	0·84	1·07
$Et_2N{\cdot}[CH_2]_3{-}$	5·50	7·66	6·41	0·93	1·19
$Et_2N{\cdot}[CH_2]_4{-}$	5·04	6·64	6·14	0·94	1·19
$Et_2N[CH_2]_5{-}$	4·90	6·47	6·00	0·94	1·19
$Et_2N{\cdot}[CH_2]_6{-}$	4·66	6·43	5·98	0·94	1·19
$Et_2N{\cdot}[CH_2]_7{-}$	4·44	6·27	5·77	0·94	1·19
5-(3-Diethylaminopropylamino)acridine	4·61	6·26	5·46	0·97	1·20

By applying Ilkovic's equation, *viz.*:

$$I_d = 605\ nD^{1/2}Cm^{2/3}t^{1/6}$$

it is found that only one electron is taken up at each step, indicating that the first product of reduction is a free radical. Thus, for Mepacrine itself, in a phosphate buffer of pH 7·3, at 18°, we have C, the concentration of Mepacrine in millimoles/l. = 0·0993, D, the diffusion coefficient = 4·11 cm.²/sec., m, the rate of flow of mercury = 1·36 mg./sec., and t, the drop time = 2·07 sec.

For the first step, I_d, the diffusion current = 0·185 μa.; hence, n = 1·065 electrons.

For the second step, I_d = 0·115 μa.; hence n = 0·705 electron.

The diffusion coefficient, D, was calculated from Nernst's equation, $D = RT\Lambda_0/n\mathbf{F}^2$. An approx. value of Λ_0 for Mepacrine was obtained by measuring the equivalent conductance of 10^{-3}M-Mepacrine dihydrochloride (54·7 mhos/cm.²), and by multiplying this quantity by the ratio $\Lambda_0/\Lambda_{10^{-3}M}$. for barium nitrate, a salt of the same valency type.

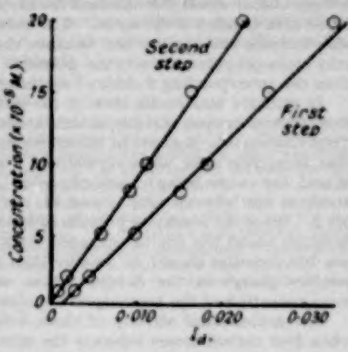
It was further found that there is a linear relation between the concentration of the acridine drug and the diffusion current to which it gives rise in the polarographic cell, for both steps of the reduction process over the concentration range 10^{-4} to 2×10^{-4}M. For the case of Mepacrine itself in buffered supporting electrolytes of pH 7·3, the results obtained are given in the table below (diffusion currents in microamps.).

Concentration, 10^{-4}M.	1	2	5	8	10	15	20
I_d, 1st step	0·029	0·044	0·104	0·153	0·185	0·260	0·329
I_d, 2nd step	0·010	0·020	0·062	0·093	0·114	0·165	0·224

The gradient of the line connecting concentration with the diffusion current of the first step (1·730 mg. cm.²/sec.) is much closer to the theoretical value (1·705) calculated from the Ilkovic equation

than is that of the second step (1·250) (see Fig. 1). In the region where there is concentration–diffusion current proportionality, the current–voltage reduction curves obtained with the polarograph may be analysed by plotting log $I/(I_d - I)$ (where I is the current at chosen, successive points on the curve) against the applied E.M.F. Such an analysis of the waves given by Mepacrine at a concentration of 10^{-4}M., in a buffer supporting electrolyte of pH 7·3, gave a linear plot for both steps of the reduction. The plot obtained from the first wave again gave a gradient (57·6 mv.) closer to the theoretical (59·1 mv.) than that obtained by the analysis of the second wave (43·8 mv.) (see Figs. 2 and 3).

FIG. 1.



pH Titrations.—Mepacrine, and all the members of the two series of acridine antimalarials here dealt with, are di-acid bases. The second dissociation constant of any of these compounds can be determined by titrating an aqueous solution of the dihydrochloride with standard alkali, the pH being measured after each addition. Owing to the precipitation of free base after the addition of one equivalent of alkali, the first dissociation constant cannot be discovered in this way, as Christophers (*Ann. Trop. Med. Parasitol.*, 1937, **31**, 43) found in the case of Mepacrine. However, the free base is quite soluble in 50% aqueous-ethanolic solution and in this medium comparative values of both dissociation constants can be found by pH titrations. In this work N-sodium hydroxide was added from a microburette to 100 c.c. of M/100-solutions of the dihydrochlorides of each homologue, the pH being found by means of a glass electrode and Cambridge pH meter after each addition of alkali. No correction was applied for sodium-ion error as comparative values of the dissociation constants were all that this enquiry demanded. The results obtained are listed in Table III, together with the values of the half-wave potentials (reduction potentials), measured at a concentration of 10^{-4}M., in buffered supporting electrolytes of pH 7·3, at 18° ± 1°.

FIG. 2.

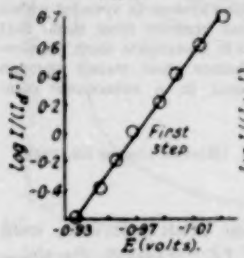
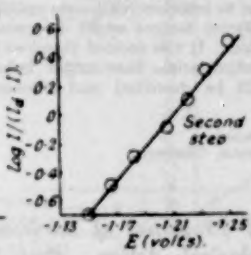


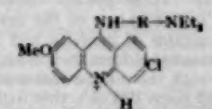
FIG. 3.



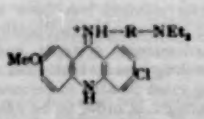
Discussion.

The polarographic measurements indicate that the first step in the reduction of Mepacrine and its analogues is probably thermodynamically reversible, since it conforms fairly closely to theoretical expectations, whilst the second would appear to be irreversible, as the deviations from theory are much larger. These views are consonant with the hypothesis that a free radical is the product of the first step, and a 5 : 10-dihydroacridine derivative the product of the second, as the former would be labile and the latter more stable (Breyer *et al.*, *loc. cit.*).

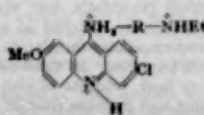
The increase in basicity with increasing length of side chain in these two series of acridine antimalarials may be ascribed to a decreasing field effect, though it is not possible to interpret this effect quantitatively in the terms used by Schwarzenbach (*Helv. Chem. Acta*, 1933, **16**, 522) for the symmetrical diamines, as the ionising powers of the two basic centres in these acridine derivatives cannot be taken as identical; further it is not possible to assign a precise location to the charge on the acridine nucleus, since the cation is probably a resonance hybrid of the forms (III) and (IV):



(III.)



(IV.)



(V.)

In the first member of each series the tertiary nitrogen atom of the side chain is separated by only two carbon atoms from the secondary nitrogen atom at position 5 of the

acridine nucleus, and thus an inductive effect down the side chain may discourage the formation of the quinonoid structure (IV), compelling the nitrogen atom at position 10 to carry a greater share of the positive charge. The lowering of the electron density round the nuclear nitrogen atom would then account for the observed lower basicity and greater ease of reduction in the first member of the series. The inductive effects of the chloro- and methoxy-substituents also decrease the basicity and enhance the cationoid activity of these compounds, as 5-[3-diethylaminopropylamino]acridine possesses a greater basicity and lower reduction potentials than the corresponding 2-chloro-7-methoxy-derivative.

In strongly acid media there is the possibility of tri-acid salt formation, as there are three basic centres in these acridine antimalarials. Christophers (*loc. cit.*) has shown that the possible third dissociation constant in Mepacrine must be greater than pK_b 11, though it is well known that Mepacrine salts, when crystallised from acid solution, contain more than two equivalents of acid, the excess being tenaciously held. If the third dissociation constant of these 5-diaminoacridines lies between pK_b 11 and 12, the tri-acid salt will predominate in buffer solutions of pH 2. Since the resonance postulated above is impossible in the tri-acid cation (V), the electron densities round the nuclear nitrogen atom in all of the homologues should be the same; the electron densities should be smaller than at other pH values where resonance "spreads" the positive charge in the di-acid cation, which might account for the fact that the half-wave potentials of the homologues are identical at pH 2, and lower than at other pH values.

The antimalarial activity of these 5-diaminoacridines reaches a maximum in both series when four carbon atoms separate the nitrogen atoms of the side chain (Kritchevski, *loc. cit.*; Magidson, *loc. cit.*). However, neither the reduction potentials nor the basicities show a maximum or minimum at this point in the series. With antimalarial drugs a simple relation between the values of some prescribed physico-chemical property and biological efficacy is hardly to be expected. In practice the drug must traverse the cellular tissue of the host and perhaps that of the parasite in order to interfere with some enzyme system or systems within the latter organism, and quite different factors might determine transfer from those that determine efficacy at the site of action. It was decided therefore to investigate those physico-chemical properties of acridine antimalarials that might influence their transit through biological material. This work will be described and discussed in a subsequent communication.

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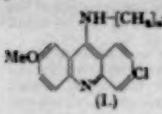
77. *Some Physico-chemical Properties of Acridine Antimalarials, with Reference to their Biological Action. Part II. Lipoid Partition Coefficients, Surface Activities, and Protein Affinities.*

By D. Ll. Hammick and S. F. Mason.

The partition coefficients of a homologous series of acridine antimalarials between vegetable oil and aqueous buffers have been measured, and have been found to be related to the basic dissociation constants of the compounds. In aqueous solution these acridine derivatives are surface-active, and the lowering of the surface tension that they produce has been determined over a range of concentrations. The relative affinities of these compounds for the protein of egg albumin have also been determined.

Attempts have been made (preceding paper) to correlate the relative antimalarial activities of six members ($n = 2$—7) of a homologous series of acridine drugs (I) with their basicities and reduction potentials, but no definite relation has been observed. These physico-chemical properties were selected as a result of general considerations as to the nature of the action of acridine antimalarials on isolated enzyme systems, and on cultures of bacteria and the malaria parasite. In these cases the drug acts on biological systems isolated from their environment or host, whereas *in vivo* a drug must be able to permeate through the cellular material of the host and perhaps that of the parasite in order to be effective at some site of action within the parasite. Thus the relative permeabilities of a structurally similar series of antimalarial drugs may affect the antimalarial activities as determined in practice. The permeability of a drug through organic material is presumably dependent on physico-chemical factors, such as the solubility of the drug, its surface activity, lipoid partition coefficient, affinity for various

proteins, and it was thought that the permeability of a given type of drug might possibly be optimum for certain values of these properties.



(I.)

The partition coefficients of six acridine antimalarials (I; $n = 2$—7) between vegetable oil and aqueous buffer solutions of pH 7·3 have been measured, as well as their surface activities and their relative affinities for the protein of egg albumin, both in M/20-phosphate buffers of pH 7·3 (the pH of blood).

Experimental.

Partition Coefficients.—Five standard solutions of the dihydrochloride of compound, covering the concentration range 10^{-4} to 10^{-5} M., were made up in M/20-phosphate buffer of pH 7·3. Each solution was divided into two parts: one was retained as a colorimetric comparator, whilst the other was shaken mechanically for 4 hours with such a volume of acid-free castor oil * as would extract between one-third and two-thirds of the acridine derivative (as indicated by preliminary experiments). The emulsion obtained was centrifuged, and the aqueous layer was then compared colorimetrically with the control solution. The latter was diluted to approx. the concentration of the extracted solution, and the comparison was repeated to guard against deviations from Beer's law. No deviations were detected, though the yellow acridine solutions did not permit of great accuracy in colorimetric comparison. Consequently the results are accurate only to within ±10%. Within these limits it was found that the ratio of the concentration of the compound in the lipoid phase to the concentration in the extracted aqueous phase

Fig. 1.

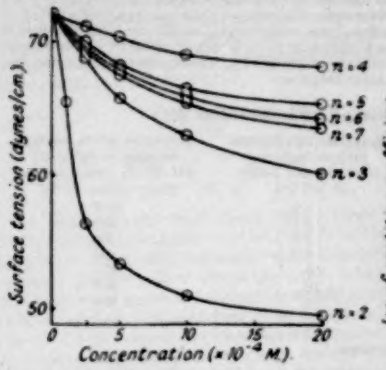
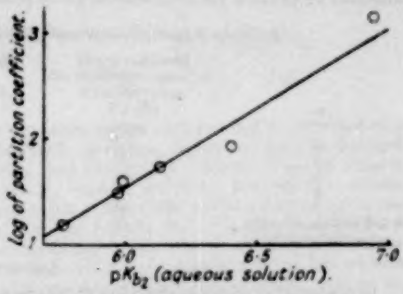


Fig. 2.



was constant for each derivative over the concentration range studied. This ratio was then taken to be the partition coefficient of the compound between vegetable oil and aqueous buffer solution of pH 7·3, the values obtained being listed in the table below.

Surface Activities.—The surface tensions of solutions of each of the prepared acridine derivatives in M/20-phosphate buffer of pH 7·3 were measured by the drop-weight method, using a stalagmometer, over the concentration range 5×10^{-4} to 2×10^{-5} M. The stalagmometer was standardised with distilled water and with the phosphate buffer, by weighing in each case ten drops that had been allowed to fall from the orifice during about a minute. The weighings were repeated several times for reproducibility, the rate of flow of liquid being maintained at a constant value throughout the measurements by means of a capillary air leak. Measurements were then carried out with the solutions of various concentrations prepared from each of the derivatives, the weight of ten drops being determined several times. The surface tension of such solutions is proportional to the weight of the drops they form at a clean orifice, and thus the tensions may be evaluated from the known surface tension of a standard, such as distilled water. The results obtained are considered to be accurate to within about ±1% and are listed in the table and Fig. 1. They are perhaps less relevant to the purposes of this enquiry than the lipoid partition coefficients and protein affinites of the compounds, as there are not likely to be many air–water interfaces in the host–parasite system, and surface activities at such interfaces bear no necessary relation to activities at other interphase boundaries, such as those between lipoid and water, which are biologically more significant.

Protein Affinities.—Perhaps the most accurate and significant measure of drug–protein affinity is afforded by dialysis experiments (Davis, *Science*, 1942, **95**, 78). A membrane, such as Cellophane, separating isotonic solutions of protein and drug, permits the diffusion of a crystalloid drug, but not of a colloidal protein. At equilibrium there is a greater concentration of drug in the protein solution than

* This work was carried out during the war when castor oil was the only vegetable oil available to the authors.

in the aqueous solution, the excess affording a measure of the drug–protein affinity. A more convenient method is the precipitation of protein from an aqueous buffer solution with alcohol in the presence of the drug (Wormall and Dewey, *Biochem. J.*, 1946, **40**, 119). The relative amount of the drug carried down with the protein may then be taken to be a measure of the drug-protein affinity.

Both of these methods have been tried with one of the acridine homologues ($n = 4$) at six different concentrations over the range 5×10^{-4} to 2×10^{-3} M. in M/30-phosphate buffers of pH 7·3. In the dialysis experiments 20 c.c. of the buffered acridine solution were placed in a short boiling-tube fitted with a cork through which passed a piece of glass tubing closed at the lower end by a Cellophane membrane and at the upper end by a rubber bung. Into this tubing were pipetted 5 c.c. of an isotonic solution containing 5% by weight of crystalline egg albumin in a buffer of pH 7·3. The dialysis tubes were then kept in a refrigerator for two weeks, after which the experimental acridine drug solutions were compared colorimetrically with control solutions.

In the alcohol-precipitation experiments 5 c.c. of the same protein solution were added to 5 c.c. of a standard acridine drug solution in phosphate buffer. After some 30 minutes, 10 c.c. of ethyl alcohol were added, and the precipitated protein was centrifuged. The supernatant aqueous-alcoholic solution was then compared colorimetrically with a control that had been appropriately diluted with phosphate buffer and alcohol.

By both methods it was found that the amount of drug taken up by the protein was directly proportional to the drug concentration in the buffer solution up to concentrations of 5×10^{-4} M. under the conditions described above. The proportionality factors were very nearly the same in both cases, and were taken as measures of the drug–protein affinity. The protein affinities of the other members of the homologous series were then determined by the alcohol-precipitation method, as this was the more convenient. The partition of each derivative between protein and aqueous buffer was measured under comparable conditions by the means described above, at four concentrations over the range 5×10^{-5} to 5×10^{-4} M. where direct proportionality between the amount of drug taken up by the protein and the drug concentration in the residual solution had been observed. The ratio of these two quantities was then taken as the protein affinity of the compound under the given experimental conditions, and the values obtained were referred to the protein affinity of the homologue ($n = 2$) taken as unity. The results obtained are listed in the table. They are accurate only to within ±10%, the limiting factor being the sensitivity of the eye in the comparison of yellow acridine solutions.

2-Chloro-5-(ω-diethylaminoalkylamino)-7-methoxyacridine (I).

n.	Partition coeffs. between vegetable oil and buffer of pH 7·3.	Relative distribution factors between albumin and buffer of pH 7·3.	Lowering of the surface tension of buffer of pH 7·3 in dynes/cm. at drug concn. 10^{-3} M.
2	1600	1·0	21·0
3	82	2·1	9·0
4	34	2·7	3·0
5	43	0·8	5·5
6	31	14	6·0
7	15	17	6·6
5-(3-Diethylaminopropylamino)acridine	22	15	6·4

Discussion.

In general the lyophobic character of organic compounds tends to increase with chain length in a homologous series, but in the case of the acridine homologues studied in the present work this relation did not hold. This may possibly be ascribed to the fact that under the experimental conditions at which measurements of oil–water partition coefficients were made, *i.e.*, at pH 7·3, these 5-diaminoacridines exist in the form of univalent and bivalent cations, the ratio of the two forms being determined by the value of pK_{i_2} for aqueous solutions. A plot of the logarithms of the partition coefficients for the series against the values of pK_{i_2} ($-\log K_{i_2}$) for aqueous solutions (preceding paper) gives a straight line with a slope of 1·6 (Fig. 2), indicating an inverse proportionality of this power between the vegetable-oil partition coefficient and the second dissociation constant of this particular type of compound at pH 7·3.

The surface activities and protein affinities of the acridine homologues seem not to be related in any definite way with other physico-chemical properties or structural features of the series. However, the relative values of these properties do seem to be related to the biological activities of the compounds, and in a subsequent communication these possible relations are discussed.

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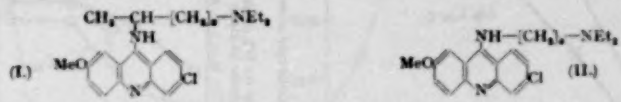
78. *Some Physico-chemical Properties of Acridine Antimalarials, with Reference to their Biological Action. Part III. The Correlation of Physico-chemical Properties with Biological Action.*

By S. F. Mason.

The degree to which members of two homologous series of acridine antimalarials (I and II) inhibit the enzyme system, diamine-oxidase, has been found to parallel the values of the reduction potentials of these compounds. No definite correlation between their antimalarial activities and their physico-chemical properties has been discovered, but an explanation of the order of their activities has been suggested, in terms of (*a*) the factors that possibly determine the permeability of these drugs through organic material, and (*b*) the equilibrium distribution of these compounds amongst the various organic phases within an organism, namely, their lipoid partition coefficents, surface activities, and relative protein affinities.

In Part I of this series (p. 345) an attempt was made to relate the antimalarial activities of two homologous series of acridine drugs (I and II) with their reduction potentials and basicities, but no relation was observed. This was ascribed to the complexity of antimalarial activity *in vivo*. A given drug must permeate through the cellular tissue of the host and perhaps of the parasite in order to interfere with some enzyme system, or systems, within the parasite, and *en route* may become distributed amongst the various phases, aqueous, lipoid, and protein, of both organisms, so that only a small concentration of the drug is present at the site of action. Thus the "antimalarial activities" of a series of drugs, as determined *in vivo*, may be a combination of their relative permeabilities and distribution factors, as well as of their relative potencies at the site of action.



It was thought that these two aspects of antimalarial activity might be separated for individual treatment, and in Part II of this series (preceding paper) the physico-chemical properties that might influence the permeability and distribution of these drugs in organic systems, namely, their lipoid partition coefficients, surface activities, and relative protein affinities, were measured for all members of series (II). The other factor contributing to the relative antimalarial activities of such a series of drugs, namely, their relative efficacies at the site of action, cannot be investigated physico-chemically at all fully as insufficient is known at present concerning the mode of action of 5-diaminoacridine antimalarials on the malaria parasite and other biological systems. However the physico-chemical properties chosen for investigation in Part I were selected by considering such knowledge as we have on this subject, the conclusion being reached that the reduction potentials and basicities of the acridine homologues (I and II) might be related to their activities on some simple biological system, such as an enzyme system, which would be free from the complication of the relative permeability and distribution factor.

Use was therefore made of the fact that 5-diaminoacridines inhibit the oxidation of diamines by diamine-oxidase. The concentrations required to inhibit this enzyme system to the extent of 50% were measured in the case of each of the acridine homologues (I and II), the values obtained being listed in Table I below.* This particular enzyme system was chosen because it might possibly be one of the vital activities of the malaria parasite that is suspended by acridine antimalarials analogous to Mepacrine (I; $n = 3$). Compounds of this type, to which all the derivatives used in the present work belong, are diamines, and thus might be expected to inhibit the utilisation of a structurally similar (diamine) metabolite by a biological organism. Furthermore Silverman and Evans (*J. Biol. Chem.*, 1944, **154**, 521) have shown that polyamines restore growth to cultures of bacteria inhibited by Mepacrine, and have demonstrated competitive antagonism between Mepacrine and polyamines in this connection.

This is not to suggest of course that the figures quoted for the inhibition of the diamine-oxidase system by our acridine derivatives provide a measure of their relative efficacies at the

* The author is indebted to members of the Pharmacology Department, Oxford, for these measurements; notably to Dr. Duthie, who studied the four members of the branched-chain homologues (I), and to Dr. Blaschko, who investigated the six members of the straight-chain series (II).

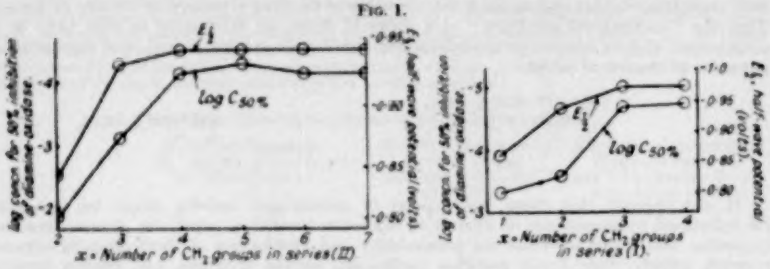
site of action within the malaria parasite, for there is no evidence as yet that the inhibition of diamine-oxidase is even a necessary, much less a sufficient, cause of antimalarial action.

TABLE I.

	x	$E_{\frac{1}{2}}$, 1st step, v.	Concentration required to produce 50% inhibition of diamine oxidase, M.	$E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log C_{50\%\ \text{inhib.}}$ n = 1, v.	n = 2, v.
Series II.	2	−0·84	$1{\cdot}45 \times 10^{-4}$	−0·73	−0·79
	3	−0·93	$7{\cdot}5 \times 10^{-4}$	−0·75	−0·84
	4	−0·94	$6{\cdot}5 \times 10^{-5}$	−0·70	−0·82
	5	−0·94	5×10^{-5}	−0·69	−0·82
	6	−0·94	$6{\cdot}5 \times 10^{-5}$	−0·70	−0·82
	7	−0·94	$6{\cdot}5 \times 10^{-5}$	−0·70	−0·82
Series I.	1	−0·86	5×10^{-4}	−0·67	−0·75
	2	−0·94	3×10^{-4}	−0·74	−0·84
	3	−0·97	2×10^{-4}	−0·70	−0·84
	4	−0·97	$1{\cdot}7 \times 10^{-4}$	−0·70	−0·84

The first half-wave potentials (oxidation–reduction potentials) of these acridine homologues parallel to some degree the logarithms of the concentrations required to bring about 50% inhibition of the diamine-oxidase system (Fig. 1). Some connection between these two

FIG. 1.



properties is perhaps to be expected since the system inhibited is concerned with oxidation, a process in which the oxidation–reduction characteristics of an inhibitory drug might be operative. The potential of an oxidation–reduction system, such as one of these acridine drugs present in both an oxidised and a reduced form, is governed by the equation :

$$E = E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log \frac{C_{\text{red.}}}{C_{\text{oxid.}}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

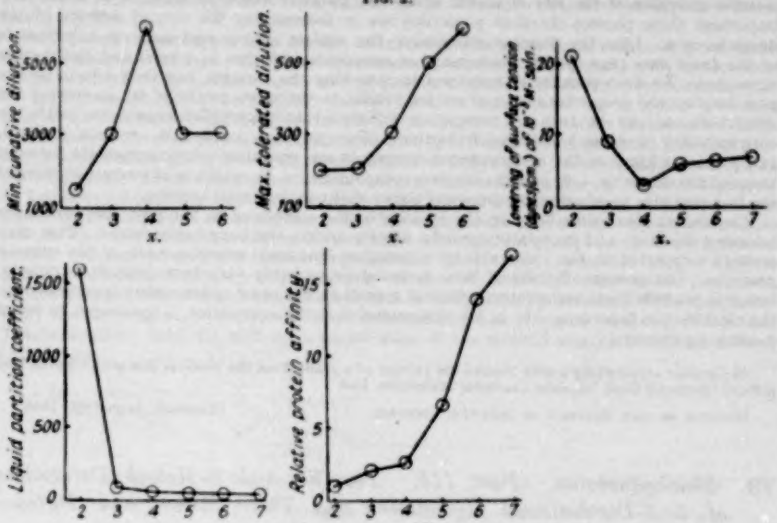
which may be rearranged $$E - \frac{RT}{nF} \cdot \log C_{\text{oxid.}} = E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log C_{\text{red.}} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

It is found that the quantity, $E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log C_{50\%\ \text{inhib.}}$, has approximately the same value for each compound when $n = 1$, $n = 2$ electrons (Table I), the best constancy being obtained when $n = 1{\cdot}5$. This relation is curious, since it may be taken to imply that most of the drug used in inhibiting the diamine-oxidase system exists in the semi-reduced and fully reduced forms under conditions where the enzyme system is inhibited to the extent of 50%. It would also imply (equation 2) that the quantity, $E - \frac{RT}{nF} \cdot \log C_{\text{oxid.}}$, has approximately the same value for each compound in these conditions. Thus if it be assumed that a small constant quantity of the drug remains in the oxidised form, the determinant of a given degree of diamine-oxidase inhibition with these 5-diaminoacridines might be said to be the setting up of an oxidation–reduction system with a definite potential E, as lower half-wave potentials would be compensated by larger concentrations of the drug added to the enzyme system and passing into the reduced forms.

It is difficult to obtain a quantitative measure of antimalarial activity that is at all definitive, since numerical values obtained vary somewhat with the method of determination. However,

the relative activities of the members of the two series (I and II) can be shown qualitatively, and it has long been accepted that the most active members of both series are those in which four carbon atoms separate the two nitrogen atoms of the side chain. The antimalarial data listed in Table II are taken from Magidson (*Ber.*, 1936, **69**, 396), the minimum curative dilution being a measure of the antimalarial activity of the derivative *in vivo*, and the maximum

FIG. 2.



x = *number of methylene groups in series* (II).

tolerated dilution a measure of its toxicity to the host; the physico-chemical data are taken from Part II of this series.

TABLE II.

Compounds (II).

x.	Maximum tolerated dilution.	Minimum curative dilution.	Partition coeffs. between vegetable oil and buffer of pH 7·3.	Relative distribution factors between albumin and buffer of pH 7·3.	Lowering of the surface tension of buffer of pH 7·3 in dynes/cm.[3] at drug concn. 10^{-3} M.
2	200	1500	1600	1·0	21·0
3	200	3000	82	2·1	9·0
4	300	6000	54	2·7	3·0
5	500	3000	43	6·8	5·5
6	600	3000	31	14	6·0
7	*	—	15	17	6·6
5-(3-Diethylaminopropyl amino)acridine	†	—	22	15	6·4

* Tested through the courtesy of I.C.I. (Pharmaceuticals) Ltd. and found inactive at a dose of 4 mg. per 50 g. of body weight of host.

† Slightly active (Mietzsch, *Angew. Chem.*, 1934, **47**, 416).

Table II and the curves on Fig. 2 show that the antimalarial activities of the acridine homologues *in vivo* do not vary in the same way as their activities against the enzyme, diamine-oxidase, indicating that factors determining transfer and distribution in biological systems may be significant in determining their overall antimalarial action *in vivo*. It would appear (Table II) that the effectiveness of the 5-diaminoacridine type of antimalarial drug is enhanced

by those properties that ensure a comparatively high equilibrium concentration of the drug in the aqueous phases of the host–parasite system. Homologues with high lipoid partition coefficients, large protein affinities, and, less significantly, high surface activities at air–water interfaces, are those which are less active against the malaria parasite. Thus the variation of these properties with the length of side chain may go some way towards explaining the variation of antimalarial activity from homologue to homologue, though a knowledge of their relative activities at the site of action within the parasite would be required to assess how important these physico-chemical properties are in determining the overall activity of the drugs *in vivo*. Like the diamine side-chains, the nuclear chloro- and methoxy-substituents of the drugs may play specific biochemical or stereochemical roles in transit and distribution throughout the host–parasite system, and in attacking the parasite, but their effects on the physico-chemical properties of the drugs are similar to variations produced by shortening the side chain, as can be seen by comparing 5-(3-diethylaminopropylamino)acridine with the corresponding 2-chloro-7-methoxy-derivative. The partition coefficient, surface activity, and protein affinity of the unsubstituted compound are quantitatively intermediate between those of the active ($x = 6$) and the inactive compound ($x = 7$), which is of interest in view of the fact that this unsubstituted compound shows slight antimalarial activity.

Correlation also exists between the toxicity of the compound to the host (the maximum tolerated dilution) and its relative protein affinity within the homologous series. This may perhaps be related to the vulnerability of complex functional proteins, such as the enzyme proteins. The protein affinities of these homologues probably vary from protein to protein, but it is possible that their relative affinities remain in the same order, unless specific stereochemical factors intervene. It is for this reason that the correlation is considered to be of possible significance.

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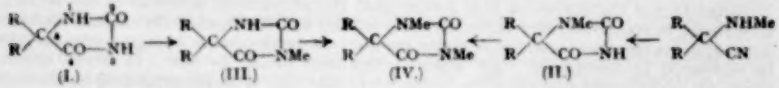
79. *Thiohydantoins. Part III. The N- and S-Methyl Derivatives of 5 : 5-Disubstituted Hydantoins and Their Mono- and Di-thio-analogues.*

By H. C. Carrington and W. S. Waring.

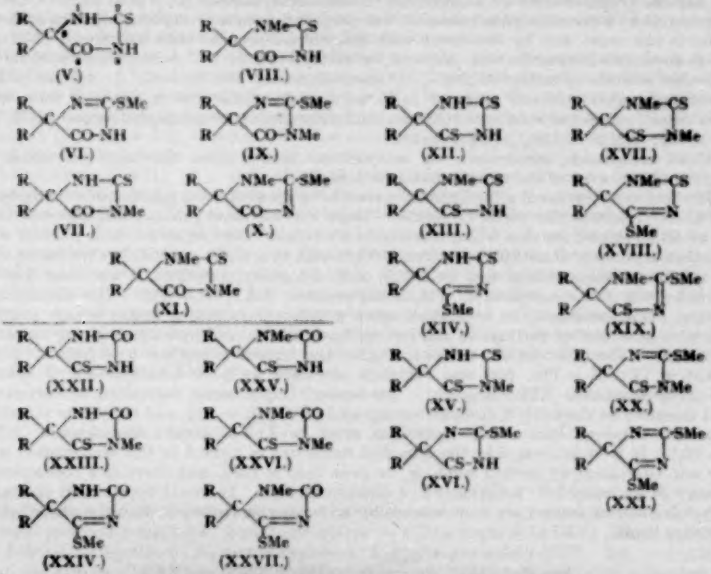
Examples have been provided of all the possible types of *N*- and *S*-methyl derivatives of 5 : 5-disubstituted hydantoins and their mono- and di-thio-analogues with the single exception of the 4-thio-2-methylthio-1-methyl derivatives. The experiments have been carried out in the 5 : 5-diphenyl and 5 : 5-pentamethylene series, and the results have been closely similar, but a few minor differences have been observed. The experimental methods used were simple, namely, methylation by methyl iodide, methyl sulphate, or diazomethane, replacement of oxygen by sulphur by the action of phosphorus pentasulphide, removal of methylthio-groups by acid hydrolysis, and replacement of sulphur by oxygen by the action of 2-aminoethanol followed by acid hydrolysis as described in Part II (Carrington, *J.*, 1947, 684).

Although a considerable amount of information on the alkylation of hydantoins is available, no systematic study of the various possible methyl derivatives of 5 : 5-disubstituted hydantoins and their thio-analogues has yet been made. It is well known that the alkali-soluble 5 : 5-disubstituted hydantoins (I) are readily methylated by the usual reagents to give the 3-methyl derivatives (III), which are converted by further, somewhat more drastic methylation into the 1 : 3-dimethyl derivatives (IV). The 1-methyl-5 : 5-disubstituted hydantoins (II) are not obtained by direct methylation, but are usually synthesised from the corresponding α-methylamino-nitriles by the action of cyanate, with subsequent hydrolysis. The 1-methyl derivatives, unlike the 3-methyl compounds, are soluble in alkali, and readily undergo further methylation to the 1 : 3-dimethyl derivatives. There appears to be no description of *O*-methylation occurring during the methylation of hydantoin derivatives.



When we consider the thiohydantoins, however, the formation of *S*-methyl derivatives must be taken into account, and the number of possible products is greatly increased. Thus with the 5 : 5-disubstituted-2-thiohydantoins (V) there are formally possible three monomethyl derivatives (VI—VIII) and three dimethyl derivatives (IX—XI). The corresponding 4-thiohydantoins (XXII) may lead to three possible monomethyl derivatives (XXIII—XXV) and two dimethyl derivatives (XXVI and XXVII), while the 2 : 4-dithiohydantoins (XII) may give rise to four monomethyl derivatives (XIII—XVI) and no less than five dimethyl derivatives (XVII—XXI).

The present experiments have set out to investigate how far these numerous possibilities can be realised in practice. They have been carried out, for the most part, with two series of compounds, the 5 : 5-diphenyl- and the 5 : 5-pentamethylene-hydantoins. In the first series the parent compound, 5 : 5-diphenylhydantoin itself, is well known, being widely used as a drug in the treatment of epilepsy. Several other members of this series are also known. Biltz, in his study of the reaction between benzil and urea and its derivatives, prepared 5 : 5-diphenyl-3-methylhydantoin (*Ber.*, 1908, **41**, 1386) and 5 : 5-diphenyl-1 : 3-dimethylhydantoin (*ibid.*, pp. 170, 1379). Similar experiments with thiourea and its derivatives led to 5 : 5-diphenyl-, 5 : 5-diphenyl-3-methyl-, and 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin, and it was also shown that methylation of the corresponding thio-compounds with methyl sulphate could give rise to the methylthio-derivatives 2-methylthio-4-keto-5 : 5-diphenyl- and 2-methylthio-4-keto-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (*idem*, *ibid.*, 1909, **42**, 1792). 5 : 5-Diphenyl-2 : 4-dithiohydantoin was prepared by Henze and Smith (*J. Amer. Chem. Soc.*, 1943, **65**, 1090) by the action of phosphorus trisulphide on the parent hydantoin. While the present work was in progress 5 : 5-diphenyl-1-methylhydantoin was prepared by Long, Miller, and Troutman (*ibid.*, 1948, **70**, 902) by a modification of the method usually used for 1-methylhydantoins.



In the 5 : 5-pentamethylenehydantoin series the parent compound was prepared by Bucherer and Lieb (*J. pr. Chem.*, 1934, **141**, 5) during their pioneer development of new hydantoin syntheses. The corresponding 2-thio-, 4-thio-, and 2 : 4-dithio-hydantoins were described in the earlier papers of this series (Carrington, *J.*, 1947, 681, 684).

Comparatively few experimental procedures have been employed in the present study.

Methylations have been carried out using methyl iodide, methyl sulphate, and diazomethane. Phosphorus pentasulphide has been used for the replacement of oxygen by sulphur, and the reverse replacement of sulphur by oxygen has been accomplished by the action of 2-aminoethanol and subsequent hydrolysis of the 2-hydroxyethylimino-derivatives as described in Part II (*loc. cit.*). Alternatively, sulphur, where present in the form of methylthio-groups, has been removed by direct acid hydrolysis. By applying various permutations and combinations of these procedures it has been possible to synthesise nearly all the possible methyl derivatives.

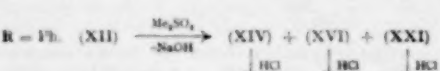
Most of the experiments have been carried out in both the 5 : 5-diphenyl- and the 5 : 5-pentamethylene hydantoin series, and the results have been closely parallel. Only in a few cases have minor differences in behaviour been observed, and attention will be drawn to these. It is proposed to describe first the synthesis of some key reference compounds and then to discuss the more complicated methylations.

5 : 5-Diphenyl-1-methylhydantoin (II; R = Ph) was prepared both by the method of Long, Miller, and Troutman (*loc. cit.*) and by an alternative method which will be described later. Several other routes to the 5 : 5-diphenyl-1-methylhydantoin series were also investigated. α-Chlorodiphenylacetamide (Steinkopf, *Ber.*, 1908, **41**, 3593) was converted by methylamine in benzene into *α-methylaminodiphenylacetamide*, but attempts to cause this to react with carbon disulphide to give 5 : 5-diphenyl-1-methyl-2-thiohydantoin failed. Again, 5 : 5-diphenylhydantoin with benzyl chloride in aqueous-alcoholic alkali gave 5 : 5-*diphenyl*-3-*benzylhydantoin*, which was further substituted by reaction with methyl sulphate to give 5 : 5-*diphenyl*-1-*methyl*-3-*benzylhydantoin*, but attempts to remove the benzyl group by catalytic hydrogenation were unsuccessful. Treatment of 5 : 5-diphenyl-1-methylhydantoin with phosphorus pentasulphide in boiling tetralin gave 5 : 5-*diphenyl*-1-*methyl*-2 : 4-*dithiohydantoin* (XIII; R = Ph). 5 : 5-Diphenyl-3-methylhydantoin (III; R = Ph) gave similarly 5 : 5-*diphenyl*-3-*methyl*-2 : 4-*dithiohydantoin* (XV; R = Ph). 5 : 5-*Diphenyl*-1 : 3-*dimethyl*-2 : 4-*dithiohydantoin* (XVII; R = Ph) was likewise prepared from 5 : 5-diphenyl-1 : 3-dimethylhydantoin (IV; R = Ph).

1-*Methyl*-5 : 5-*pentamethylenehydantoin* was prepared from α-methylaminohexahydrobenzonitrile in the usual way by treatment with cyanate followed by acid hydrolysis. 3-*Methyl*-5 : 5-*pentamethylenehydantoin* was prepared by methylation of 5 : 5-pentamethylenehydantoin in alkaline solution by methyl sulphate. Diazomethane may also be used. 1 : 3-*Dimethyl*-5 : 5-*pentamethylenehydantoin* was prepared from the 1-methyl-hydantoin in either of these ways. These three hydantoins were converted into the corresponding 2 : 4-*dithiohydantoins* (XIII, XV, and XVII; RR = $<[CH_2]_5$, respectively).

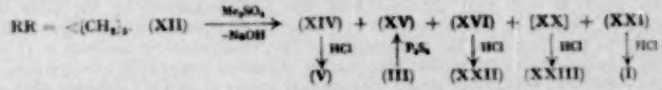
These compounds, synthesised by unequivocal routes, form the basis on which the identification of most of the other derivatives depends.

The first methylation of a thiohydantoin studied in detail was the reaction of 5 : 5-diphenyl-2 : 4-dithiohydantoin with methyl sulphate. There were obtained an alkali-insoluble substance, and an alkali-soluble fraction which was clearly a mixture. The alkali-insoluble product was a colourless crystalline dimethyl derivative. When acid hydrolysis resulted in elimination of all the sulphur as methanethiol and formation of 5 : 5-diphenylhydantoin, it was clear that this derivative was 2 : 4-*dimethylthio*-5 : 5-*diphenylglyoxaline* (XXI; R = Ph). The alkali-soluble fraction, on chromatographic separation, gave a pale yellow and a bright orange product; both were monomethyl derivatives and lost methanethiol on acid hydrolysis, giving monothiohydantoins. The pale yellow compound gave the known colourless 5 : 5-diphenyl-2-thiohydantoin (V; R = Ph), and was therefore identified as 2-*thio*-4-*methylthio*-5 : 5-*diphenyl*-2 : 5-*dihydroglyoxaline* (XIV; R = Ph). The isomeric bright orange derivative, by elimination, must therefore be the 4-*thio*-2-*methylthio*-compound (XVI; R = Ph), and the yellow monothiohydantoin obtained from it on hydrolysis must be 5 : 5-*diphenyl*-4-*thiohydantoin* (XXII; R = Ph). It is of interest that the dimethyl derivative is formed in this methylation when only one equivalent of methyl sulphate, or even less, is used, and there is a corresponding recovery of unchanged 5 : 5-diphenyl-2 : 4-dithiohydantoin. It would appear that the monomethyl derivatives formed are more susceptible to further methylation than the unmethylated substance itself.



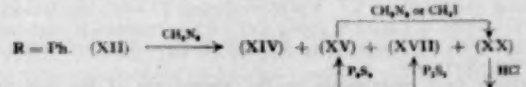
Some preliminary experiments on the methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin were described in Part II. There the main product isolated after removal of alkali-

insoluble material and acidification of the remainder was identified as 5 : 5-pentamethylene-4-thiohydantoin. A more detailed study which has now been made showed that the alkali-insoluble product was mainly 2 : 4-*dimethylthio*-5 : 5-*pentamethyleneglyoxaline*, identified by acid hydrolysis to 5 : 5-pentamethylenehydantoin. This was probably accompanied by a little (XX; RR = $<[CH_2]_5$), for acid hydrolysis of the crude product gave also an alkali-insoluble substance later identified as 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII; RR = $<[CH_2]_5$). The alkali-soluble fraction was isolated by careful acidification with phosphoric acid, and on chromatographic separation gave three products, first, 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin, identical with that obtained by introduction of sulphur into the corresponding hydantoin, secondly, 4-*thio*-2-*methylthio*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (XVI; RR = $<[CH_2]_5$), identified by acid hydrolysis to 5 : 5-pentamethylene-4-thiohydantoin (XXII), and thirdly, the 2-*thio*-4-*methylthio*-isomer (XIV), which was identified both by acid hydrolysis to 5 : 5-pentamethylene-2-thiohydantoin (V; RR = $<[CH_2]_5$), and by reaction with 2-aminoethanol to give 4-2′-hydroxyethylimino-5 : 5-pentamethylene-2-thiohydantoin, identical with that described in Part II (*loc. cit.*). As in the 5 : 5-diphenylhydantoin series, there was also some unchanged starting material.



The main differences between the two series were, first, the slight tendency to *N*-methylation in the 3-position in the 5 : 5-pentamethylene series, and secondly, the variation in the proportion of the two monomethylthio-derivatives produced. In the 5 : 5-diphenyl series, the 4-methylthio-compound predominated, while in the 5 : 5-pentamethylene series there was more of the 2-methylthio-derivative. In the 5 : 5-pentamethylene series, the 4-thiohydantoin was the main alkali-soluble product when the acidification took place under such conditions as would bring about the hydrolysis of the very labile 2-methylthio-group.

The methylation of 5 : 5-diphenyl-2 : 4-dithiohydantoin with diazomethane gave rather different results. There were obtained two monomethyl and two dimethyl derivatives. The former were the 2-thio-4-methylthio-compound (XIV; R = Ph), the only product common to the methyl sulphate and diazomethane methylations, and 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV; R = Ph), identical with that obtained by introduction of sulphur into 5 : 5-diphenyl-3-methylhydantoin. The dimethyl derivatives were 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII; R = Ph), identical with that obtained from 5 : 5-diphenyl-1 : 3-dimethylhydantoin, and a new, pale yellow, crystalline compound, the structure of which was established as follows. It was identical with a dimethyl derivative obtained by the further methylation of 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV; R = Ph) either by methyl iodide or by diazomethane. Only two dimethyl derivatives could be derived by the further methylation of this compound. One of these was the 1 : 3-dimethyl compound (XVII; R = Ph) already identified, and the new compound must therefore be the other, 4-*thio*-2-*methylthio*-5 : 5-*diphenyl*-3-*methyl*-4 : 5-*dihydroglyoxaline* (XX; R = Ph). Confirmation of this structure was obtained by acid hydrolysis, methanethiol being evolved and a monomethyl monothio-derivative of diphenylhydantoin obtained which must clearly be 5 : 5-*diphenyl*-3-*methyl*-4-*thiohydantoin* (XXIII; R = Ph).



Methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin by diazomethane gave as the main products 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV; RR = $<[CH_2]_5$) and 2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5 dihydroglyoxaline (XIV; RR = $<[CH_2]_5$). There was also an oily fraction of dimethyl derivatives which was not completely separated into its constituents, but which gave on acid hydrolysis 3-*methyl*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXIII; RR = $<[CH_2]_5$) thus indicating the presence of the 2-methylthio-3-methyl-4-thio-derivative, analogous to that obtained in the 5 : 5-diphenylhydantoin series.

The methylation of 5 : 5-diphenyl-2 : 4-dithiohydantoin in aqueous-alcoholic sodium hydroxide with one equivalent of methyl iodide gave a mixture of the 2-thio-4-methylthio-

(XIV; R = Ph) and the 2 : 4-dimethylthio-compound (XXI; R = Ph), with a recovery of some unchanged starting material. Methylation in alcoholic solution with an excess of methyl iodide and in the presence of sodium hydrogen carbonate gave the 2 : 4-dimethylthio-derivative, or, if the reaction was carried out at a higher temperature and without efficient stirring, *4-methylthio-2-keto-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XXIV; R = Ph). The structure of this compound was proved by its reaction with aqueous 2-aminoethanol to give *4-2′-hydroxyethylimino-5 : 5-diphenylhydantoin* identical with that produced from 5 : 5-diphenyl-4-thiohydantoin by the same reagent. The formation of (XXIV) during this methylation clearly resulted from a partial hydrolysis of the preformed 2 : 4-dimethylthio-derivative, and this hydrolysis was, in fact, accomplished by careful treatment of 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline with 80% acetic acid.

In the methyl iodide methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin, loss of methanethiol occurred even more readily, and the only product isolated was *4-methylthio-2-keto-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XXIV; RR = $<[CH_2]_5$), identical with the product obtained by the action of methyl iodide on 5 : 5-pentamethylene-4-thiohydantoin. Its structure was confirmed (*a*) by conversion into 4-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, identical with that obtained from the 4-thiohydantoin by the same method (Carrington, *J.*, 1947, 684), and (*b*) by acid hydrolysis to 5 : 5-pentamethylenehydantoin.

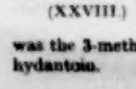
To complete the account of the methylation of the dithiohydantoin derivatives, it remains to describe experiments on the further methylation of various monomethyl derivatives. 5 : 5-Diphenyl-1-methyl-2 : 4-dithiohydantoin with methyl iodide or methyl sulphate gave mainly *4-methylthio-2-thio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XVIII; R = Ph) (evidence for this structure will be discussed later), accompanied by a little 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin. The methylation of 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin with methyl iodide or diazomethane to give the 4-thio-2-methylthio-derivative has already been mentioned. 2-Thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline with diazomethane gave the 2 : 4-dimethylthio-derivative.

Methylation of 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin has been studied using all three reagents, and in all cases the 1 : 3-dimethyl- and the *4-methylthio-1-methyl*-compound (XVIII; RR = $<[CH_2]_5$) were obtained. The proportions of the two products, however, varied with the methylation procedure adopted. Thus, with diazomethane the former predominated, and with methyl iodide the latter, while with methyl sulphate approximately equal amounts of each were produced. With methyl iodide there was also formed, however, a very small amount of a yellow alkali-soluble monomethyl-monothio-derivative, which it seems can, by elimination, only be *1-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXV; RR = $<[CH_2]_5$), produced by hydrolysis of preformed 4-thio-2-methylthio-1-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline. This last type, the 4-thio-2-methylthio-1-methyl-derivative, remains the only class of methylated derivative which has not been exemplified in the present work.

3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin gave *4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XX; RR = $<[CH_2]_5$) on methylation either with methyl iodide or with diazomethane. The structure of this compound was proved in a similar way to that of the corresponding 5 : 5-diphenylhydantoin derivative, by the fact that acid hydrolysis liberated methanethiol, showing the second methyl group to be attached to sulphur, and gave as product 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII; RR = $<[CH_2]_5$). The presence of this dimethyl derivative had been deduced in the product of the diazomethane methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin by a similar hydrolysis, but its isolation in a state of purity was not accomplished in that case.

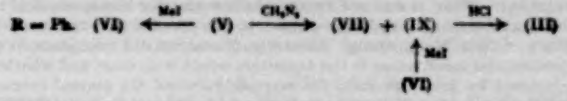
4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline with methyl iodide gave the 2 : 4-dimethylthio-derivative.

We must consider next experiments on the methylation of the monothiohydantoins. 5 : 5-Diphenyl-2-thiohydantoin (V; R = Ph), with methyl iodide in the usual way, gave 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI; R = Ph) (cf. Biltz, *loc. cit.*). This compound was also described by Cattelaine and Chabrier (*Bull. Soc. chim.*, 1947, 639) who gave it the formula (XXVIII), and stated that further methylation with methyl iodide gave 4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline, which could then be hydrolysed to 5 : 5-diphenyl-1-methylhydantoin. The present work, however, was in agreement with the observation of Biltz, and confirmed that the product of further methylation was the 3-methyl compound (IX; R = Ph), for on hydrolysis it gave 5 : 5-diphenyl-3-methylhydantoin.

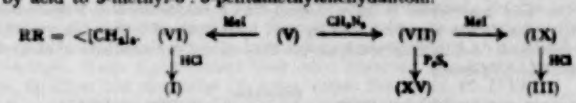


(XXVIII.)

Methylation of 5 : 5-diphenyl-2-thiohydantoin with diazomethane gave three products. In addition to 4-keto-2-methylthio-5 : 5-diphenyl- and 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline described above, there was also produced 5 : 5-diphenyl-3-methyl-2-thiohydantoin (VII; R = Ph). The other possible structure for this compound, namely 5 : 5-diphenyl-1-methyl-2-thiohydantoin, was excluded by the synthesis of this latter compound by another route which will be described later.



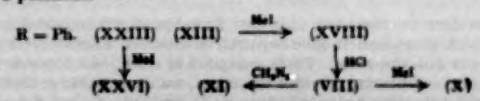
With methyl iodide 5 : 5-pentamethylene-2-thiohydantoin (V; RR = $<[CH_2]_5$) gave a result parallel to that just described for the 5 : 5-diphenyl series, *4-keto-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (VI; RR = $<[CH_2]_5$) being produced, the structure of which was proved by acid hydrolysis to methanethiol and 5 : 5-pentamethylenehydantoin. Diazomethane, however, gave only *3-methyl-5 : 5-pentamethylene-2-thiohydantoin* (VII; RR = $<[CH_2]_5$); the location of the methyl group in the 3-position was established, first, by conversion by phosphorus pentasulphide into 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin, and secondly, by further methylation with methyl iodide to give *4-keto-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (IX; RR = $<[CH_2]_5$) which was hydrolysed by acid to 3-methyl-5 : 5-pentamethylenehydantoin.



Comparatively few experiments have been carried out in the 4-thiohydantoin series. 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV; R = Ph) with methyl iodide gave the *1-methyl* derivative (XXVII; R = Ph), which was readily hydrolysed to 5 : 5-diphenyl-1-methylhydantoin. This series of reactions was of interest in that it provided another means of entry into the series of 5 : 5-diphenyl-1-methyl derivatives, which is otherwise rather difficult of access.

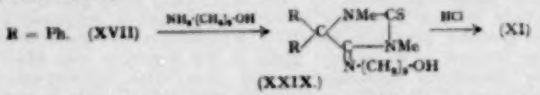
5 : 5-Pentamethylene-4-thiohydantoin, with methyl iodide, gave 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV; RR = $<[CH_2]_5$). When diazomethane was used, this product was accompanied by 3-methyl-5 : 5-pentamethylene-4-thiohydantoin, which had previously been obtained by the hydrolysis of the 2-methylthio-3-methyl-4-thio-derivative.

5 : 5-Diphenyl-3-methyl-4-thiohydantoin (XXIII; R = Ph), on treatment with methyl iodide, gave the 1 : 3-*dimethyl* derivative (XXVI; R = Ph). The establishment of the structure of this compound was of great value in settling the constitution of another derivative mentioned previously, the product obtained by the methylation of 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII; R = Ph). On acid hydrolysis, this last methylated product lost methanethiol and gave a 1-methyl-monothio-derivative, which could only be the 2- or 4-thio-compound. This was converted by diazomethane into a dimethyl-monothio-derivative, stable to acid and, therefore, with both methyl groups attached to nitrogen. As this substance was different from the 1 : 3-dimethyl-4-thiohydantoin described above, it clearly could only be 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI; R = Ph). The 1-methyl-monothio-derivative from which it was obtained must, therefore, be *5 : 5-diphenyl-1-methyl-2-thiohydantoin* (VIII; R = Ph), and the product of methylation of the 1-methyl-2 : 4-dithiohydantoin was *2-thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XVIII; R = Ph). Methylation of 5 : 5-diphenyl-1-methyl-2-thiohydantoin with methyl iodide gave *4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline* (X; R = Ph), a compound of considerable interest, since it was the only example of a dimethyl derivative substituted in both the 1- and the 2-positions.



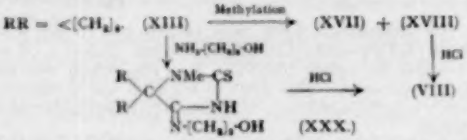
Further evidence of the structure of 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI;

R = Ph) has been obtained from its formation by another series of reactions. It was shown in Part II that when 2-aminoethanol reacted with a 5 : 5-disubstituted-2 : 4-dithiohydantoin the sulphur in the 4-position was preferentially replaced. It was further established that a 2-hydroxyethylimino-group was readily removed from the 4-position by acid hydrolysis, while in the 2-position it was unaffected by this treatment. The reaction of 2-aminoethanol with 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII; R = Ph) was therefore of considerable interest. First, it was not known whether reaction would occur at all, in view of the absence of a tautomerisable hydrogen atom : it was possible that the reaction would only take place with a $-C(SH)=N-$ grouping. Secondly, if reaction did take place, it was uncertain whether the preferential substitution in the 4-position would still occur, and whether the product would be hydrolysed by acid. In fact, the reaction followed the normal course, although it was slow, and the product, *4-2′-hydroxyethylimino-5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin* (XXIX; R = Ph) was readily hydrolysed by acid, giving 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI; R = Ph).



(XXIX.)

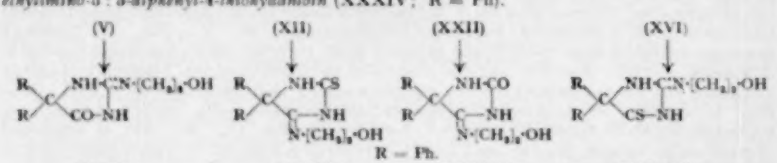
4-2′-Hydroxyethylimino-1-methyl-5 : 5-pentamethylene-2-thiohydantoin (XXX; RR = $<[CH_2]_5$) was obtained by the action of aqueous 2-aminoethanol on the 1-methyl-2 : 4-dithiohydantoin. On acid hydrolysis it gave *1-methyl-5 : 5-pentamethylene-2-thiohydantoin* (VIII; RR = $<[CH_2]_5$), which was also produced by acid hydrolysis of 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII), one of the products of methylation of the 1-methyl-2 : 4-dithiohydantoin.



(XXX.)

The action of diazomethane on 1-methyl-5 : 5-pentamethylene-2-thiohydantoin gave the 1 : 3-*dimethyl* derivative (XI). From its method of formation this could only be the 1 : 3-dimethyl or the 2-methylthio-1-methyl derivative. As it was stable to acids, and therefore contained no methylthio-group, the former structure was correct.

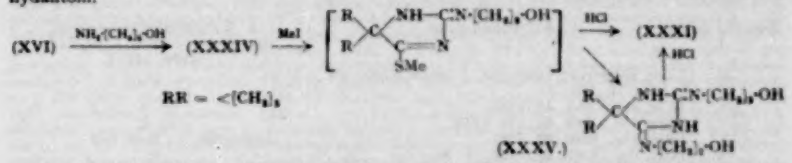
Methylthio-substituents in the hydantoin nucleus were replaced by 2-aminoethanol more readily than were the unmethylated thio-groups. Thus whereas 5 : 5-diphenyl-2 : 4-dithiohydantoin gave *4-2′-hydroxyethylimino-5 : 5-diphenyl-2-thiohydantoin* (XXXII; R = Ph), 5 : 5-diphenyl-4-thiohydantoin gave *4-2′-hydroxyethylimino-5 : 5-diphenylhydantoin* (XXXIII; R = Ph), and 5 : 5-diphenyl-2-thiohydantoin gave *2-2′-hydroxyethylimino-5 : 5-diphenylhydantoin* (XXXI; R = Ph), it was found that with 4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline reaction occurred preferentially in the 2-position, with formation of *2-2′-hydroxyethylimino-5 : 5-diphenyl-4-thiohydantoin* (XXXIV; R = Ph).



(XXXI.) (XXXII.) (XXXIII.) (XXXIV.)

It might therefore be expected that the 2 : 4-dimethylthioglyoxalines would react with 2-aminoethanol with great ease to give derivatives with two 2-hydroxyethylimino-substituents. This, however, was not the case. These compounds were inert towards 2-aminoethanol, and when, under drastic conditions, reaction did occur, no identifiable products could be isolated. A hydantoin derivative with basic substituents in both the 2- and 4-positions has, however, been obtained by an indirect route. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydro-

glyoxaline (XVI; RR = $<[CH_2]_5$) reacted readily with 2-aminoethanol to give 2-2′-*hydroxyethylimino*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXXIV; RR = $<[CH_2]_5$). This could be methylated with methyl iodide in the usual way to give 2-2′-hydroxyethylimino-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline, which was not obtained analytically pure but was characterised by acid hydrolysis with loss of methanethiol to give 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin (XXXI; RR = $<[CH_2]_5$), identical with that described in Part II. The 4-methylthio-compound now reacted readily with a second molecule of 2-aminoethanol to give 2 : 4-*di*-(2′-*hydroxyethylimino*)-5 : 5-*pentamethylenehydantoin* (XXXV; RR = $<[CH_2]_5$), which on acid hydrolysis was also converted into 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin.



RR = $<[CH_2]_5$

Another interesting reaction was the removal of methylthio-groups in the reaction with phosphorus pentasulphide. Thus, an attempt was made to find a more convenient method for the preparation of 4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (XVI; R = Ph) by the action of this reagent on the 4-keto-2-methylthio-compound, but the product obtained was 5 : 5-diphenyl-2 : 4-dithiohydantoin. A similar case was the preparation of 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin directly from 2-keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline. Such replacements have been described previously, for example, in the uracil series, by Elion and Hutchings (*J. Amer. Chem. Soc.*, 1947, **69**, 2138).

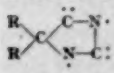
Of the twenty-seven possible types of 5 : 5-disubstituted hydantoins, their thio-analogues, and *N*- and *S*-methyl derivatives, we have thus been able to prepare representatives of all but one, namely, the 4-thio-2-methylthio-1-methyl compounds (XIX). The only case where it was possible to isolate a product with methyl groups in both the 1- and the 2-position was with 5 : 5-diphenyl-1-methyl-2-thiohydantoin, when methylation with methyl iodide occurred on the sulphur atom rather than at the 3- or 4-position.

It is not possible to formulate simple rules governing the methylation of these hydantoin derivatives, but a few general trends may be mentioned. Of the methylating agents used, methyl iodide tends to give most complete *S*-methylation. Diazomethane has the greatest tendency towards *N*-methylation, and methyl sulphate is intermediate. This is of course only to be expected, since diazomethane is used in ethereal solution, where the existence of ⁻CS·NH⁻ systems would be expected to be favoured. With the other methylating agents, the reaction was carried out in polar solvents in presence of sodium hydroxide, where ⁻C(·SH)=N⁻ systems should predominate.

There appears to be a general tendency for less *N*-methylation to occur in the 5 : 5-diphenyl series than in the 5 : 5-pentamethylene series.

An interesting contrast exists between the dithiohydantoins and the methylthio-derivatives in their behaviour towards acid. The 5 : 5-disubstituted 2 : 4-dithiohydantoins as a class are stable to acid hydrolysis, but, as described in Part II, 5 : 5-dimethyl-2 : 4-dithiohydantoin can be hydrolysed by acid to the corresponding 2-thio-derivative, the sulphur atom in position 4 being replaced by oxygen. When, however, 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline was submitted to a careful partial hydrolysis the 2-methylthio-group was removed first, leaving the 4-methylthio-group intact.

The ultra-violet absorption of the available pentamethylene derivatives has been measured in methanol solution. The hydantoins themselves show no specific absorption, but the thio-derivatives in general have characteristic bands. The structure of the dimethyl derivatives is fixed, and from their absorption spectra some deductions can be made of the probable structure of some of the unmethylated and monomethylated derivatives, where possibilities of tautomerism exist. In methanol solutions the compounds appear to exist wherever possible in the annexed form, with both the double bonds outside the ring. Thus in the dithio-series the compounds (XII), (XIII), and (XV) have spectra closely similar to that of (XVII) which must have a structure of the type indicated, and in the 2-thio-series the compounds (V), (VII), and (VIII) have spectra similar to that of (XI). In the 4-thiohydantoins there is no available compound in which this structure is obligatory.



but (XXII), (XXIII), and (XXV), with closely similar spectra, probably also exist in this form. No clear grounds appear to exist for the correlation of the structures of other members of the series with the fixed structures of (XVIII), (XX), and (XXI) on the basis of their absorption spectra in methanol solution.

Experimental.

In view of the large number of compounds involved and the fact that many of them are prepared by more than one experimental procedure, the table serves as an index to the Experimental section. References are there given for known compounds. Where alternative methods are described, the most favoured procedure is given first, followed by the others in order of preference. In the text below, cross-references given as "cf. A" etc. indicate identity established by mixed m. p. Absorption spectra were determined in methanol.

Formula no.	5 : 5-Diphenyl series.	5 : 5-Pentamethylene series.
I.	—	Bucherer and Lieb, *J. pr. Chem.*, 1934, **141**, 5.
II.	Long, Miller and Troutman, *J. Amer. Chem. Soc.*, 1948, **70**, 902; D.	G.
III.	Biltz, *Ber.*, 1909, **41**, 1386.	C, B.
IV.	Biltz, *Ber.*, 1909, **41**, 170, 1379.	C, B.
V.	Biltz, *Ber.*, 1909, **42**, 1792.	Carrington, *J.*, 1947, 684.
VI.	Biltz, *Ber.*, 1909, **42**, 1792; A, B.	A.
VII.	Biltz, *Ber.*, 1909, **42**, 1792; B.	B.
VIII.	D.	D.
IX.	Biltz, *Ber.*, 1909, **42**, 1792; A, B.	A.
X.	A.	—
XI.	Biltz, *Ber.*, 1909, **42**, 1792; F.	B.
XII.	Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090.	Carrington, *J.*, 1947, 681.
XIII.	E.	E.
XIV.	A, B, C.	B, C.
XV.	E, B.	E, B, C.
XVI.	C.	C.
XVII.	E, B, A, C.	E, B, C, A.
XVIII.	A.	A, C.
XIX.	—	—
XX.	A, B.	A, B, (C).
XXI.	A, C, B.	C, A.
XXII.	D.	Carrington, *J.*, 1947, 684.
XXIII.	D.	D, B.
XXIV.	D, A.	A, B.
XXV.	—	A.
XXVI.	A.	—
XXVII.	A, C.	—

(A) *Methylations with Methyl Iodide.*—The hydantoin (1 mol.) was suspended in methanol (or ethanol) (about 10 c.c. per g.) and aqueous sodium hydroxide (1 mol.; 12% solution) was added, whereupon the hydantoin dissolved. Alternatively, the hydantoin was dissolved in 1 equivalent of methanolic sodium hydroxide. Methyl iodide (1·1 mols.) was added and the mixture was set aside. The product usually crystallised, sometimes in a few minutes, sometimes overnight. When this failed to occur the alcohol was removed *in vacuo*, and the residue was washed with water, to remove sodium iodide, and purified by crystallisation.

In this way 5 : 5-diphenyl-2-thiohydantoin (V) gave 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI), colourless needles (from ethanol), m. p. 213° (90%) (Found : C, 67·75; H, 4·85; N, 10·1. Calc. for $C_{16}H_{14}ON_2S$: C, 68·1; H, 4·95; N, 9·95%). This (in ethanol) gave 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (IX), colourless needles (from ethanol), m. p. 178° (81%) (Found : C, 69·2; H, 5·4; N, 9·15. Calc. for $C_{17}H_{16}ON_2S$: C, 68·9; H, 5·4; N, 9·5%). 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV) (in ethanol) gave *2-keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XXVII), colourless needles (from ethanol), m. p. 229° (86%) (Found : C, 69·0; H, 5·65; N, 9·35. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). 5 : 5-Diphenyl-3-methyl-4-thiohydantoin (XXIII) (in ethanol) gave 5 : 5-*diphenyl*-1 : 3-*dimethyl*-4-*thiohydantoin* (XXVI), long cream-coloured prisms (from methanol), m. p. 211° (74%) (Found : C, 69·2; H, 5·4; N, 9·1. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). 5 : 5-Diphenyl-3-methyl-2 : 4-dithiohydantoin (XV) gave *4-thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline* (XX), pale yellow plates (from methanol), m. p. 148° (92%) (Found : C, 65·2; H, 5·2; N, 8·95. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%). 5 : 5-Diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII) (in ethanol) gave *2-thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XVIII), pale yellow needles (from methanol), m. p. 205° (82%) (Found : C, 65·3; H, 5·15; N, 9·1. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%), accompanied by a very small amount of 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII) (cf. E).

5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) gave a mixture, which on chromatographic analysis from chloroform solution on alumina gave 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI), m. p. 140° (32%; see below), *2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XIV), pale yellow plates (from ethanol), m. p. 256° (15%; this figure is probably low, owing to the difficulty of extracting this

very sparingly soluble substance from the alumina) (Found: C, 64·2; H, 4·5; N, 9·1. $C_{16}H_{12}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), and a small amount of unchanged starting material.

5 : 5-Diphenyl-1-methyl-2-thiohydantoin (VIII) gave a gummy product, which after chromatographic treatment on alumina from a solution in 1 : 1 ether–chloroform gave *4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline* (X), colourless needles (from methanol), m. p. 170° (20%) (Found: C, 68·7; H, 5·3; N, 9·7. $C_{17}H_{14}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%).

5 : 5-Pentamethylene-2-thiohydantoin (V) gave *4-keto-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (VI), colourless needles (from aqueous methanol), m. p. 152—153° (70%) (Found: C, 54·3; H, 7·1; N, 13·8. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maximum, 2370 A.; $\varepsilon = 11{,}100$. *3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XV) gave *4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XX), colourless plates (from methanol), m. p. 63—64° (75%) (Found: C, 52·6; H, 6·8; N, 12·4. $C_{10}H_{16}N_2S_3$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maxima, 2500 and 2950 A.; $\varepsilon = 8{,}900$ and 11,800 respectively. *3-Methyl-5 : 5-pentamethylene-2-thiohydantoin* (VII) gave *4-keto-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (IX), colourless prisms (from aqueous methanol), m. p. 62—63° (80%) (Found: C, 56·9; H, 7·5; N, 13·1. $C_{10}H_{16}ON_2S$ requires C, 56·6; H, 7·55; N, 13·2%); light absorption showed end absorption only. *5 : 5-Pentamethylene-4-thiohydantoin* (XXII) gave *2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XXIV), colourless prisms (from a small quantity of methanol), m. p. 236° (42%) (Found: C, 54·3; H, 7·2; N, 14·0. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maximum, 2440 A.; $\varepsilon = 9{,}820$. *4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XVI) gave *2 : 4-dimethylthio-5 : 5-pentamethyleneglyoxaline* (XXI), m. p. 48—49° (84%) (cf. C). *1-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XIII) gave *2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XVIII), yellow prisms (from methanol), m. p. 148—149° (50%) (Found: C, 52·9; H, 7·0; N, 12·0. $C_{10}H_{16}N_2S_3$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maximum, 2880 A.; $\varepsilon = 17{,}400$. There was also found a small amount of *1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XVII), m. p. 126—127° (cf. E), and a few yellow needles of an alkali-soluble substance of m. p. 188—189°, which is believed to be *1-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXV) (Found: C, 54·7; H, 7·1; N, 13·8. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%) (light absorption: Maxima, 2360 and 2850 A.; $\varepsilon = 5{,}750$ and 11,400, respectively). When the sodium salt of *5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XII) was treated with methyl iodide in methanol solution at room temperature, methahethiol was evolved; after removal of the solvent *in vacuo* the residue was washed with ether and water, and extracted with chloroform. Evaporation of the chloroform solution gave *2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XXIV), m. p. 234° (from methanol) (cf. above).

Other methylations with methyl iodide were carried out in alcoholic solution in presence of sodium hydrogen carbonate. *5 : 5-Diphenyl-2 : 4-dithiohydantoin* (XII) (7·1 g.) in methanol (100 c.c.) was heated under reflux to 50° with efficient stirring for 5 hours with methyl iodide (10 g.) and sodium hydrogen carbonate (6 g.). After the mixture had been kept overnight the product crystallised, and was filtered off, washed with water, and dried, giving *2 : 4-dimethylthio-5 : 5-diphenylglyoxaline* (XXI), long colourless prisms (from methanol), m. p. 140° (88%) (Found: C, 65·3; H, 5·35; N, 8·6. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%) (cf. above). Under slightly more vigorous conditions and without efficient stirring, a different product was obtained. Thus, (XII) (7·1 g.) in methanol (100 c.c.) was heated under reflux at 60—70° with methyl iodide (8·5 g.) and sodium hydrogen carbonate (5 g.) for 6 hours without stirring. After cooling the crystalline product was filtered off to give *2-keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XXIV), colourless prisms (from ethanol), m. p. 264° (32%) (cf. D).

(B) *Methylations with Diazomethane.*—The hydantoin was added to excess of an ethereal solution of diazomethane. In some cases a little methanol was added. The mixture was set aside overnight, and the product was isolated by removal of excess of diazomethane and ether by distillation.

5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) gave a complex mixture of products from which, by chromatographic separation of a chloroform solution on alumina, there were isolated: *4-thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline* (XX), m. p. 148° (42%) (cf. A), *5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin* (XV), m. p. 206° (20%) (cf. E), *2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XIV), m. p. 258° (15%) (cf. A), and *5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin* (XVII), m. p. 167° (2%) (cf. E). The proportion of the mono- and di-methyl derivatives obtained probably depends upon the amount of diazomethane in excess. *2-Thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XIV) gave *2 : 4-dimethylthio-5 : 5-diphenylglyoxaline* (XXI), m. p. 140° (40%) (cf. A). *5 : 5-Diphenyl-3-methyl-2 : 4-dithiohydantoin* (XV) gave *4-thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline* (XX), m. p. 148° (75%) (cf. A). *5 : 5-Diphenyl-2-thiohydantoin* (V) gave a mixture, separated by passage of its ethereal solution through an alumina column, into *4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline* (IX), m. p. 175° (5%) (cf. A), *5 : 5-diphenyl-3-methyl-2-thiohydantoin* (VII), colourless needles (from ethanol), m. p. 188° (25%) (Found: C, 68·1; H, 5·2; N, 10·0. Calc. for $C_{16}H_{14}ON_2S$: C, 68·1; H, 4·95; N, 9·95%), and *4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline* (VI), m. p. 212° (7%) (cf. A).

5 : 5-Pentamethylenehydantoin (I) gave *3-methyl-5 : 5-pentamethylenehydantoin* (III), m. p. 213° (93%) (cf. C). *1-Methyl-5 : 5-pentamethylenehydantoin* (II) gave *1 : 3-dimethyl-5 : 5-pentamethylenehydantoin* (IV), m. p. 68—69° (cf. C). *5 : 5-Pentamethylene-2-thiohydantoin* gave *3-methyl-5 : 5-pentamethylene-2-thiohydantoin* (VII), colourless plates (from methanol), m. p. 174—175° (78%) (Found: C, 54·8; H, 7·1; N, 14·3. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maxima, 2320 and 2670 A.; $\varepsilon = 9{,}380$ and 18,000 respectively. *5 : 5-Pentamethylene-4-thiohydantoin* (XXII) gave a mixture of *2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XXIV), m. p. 234° (50%) (cf. A), and *3-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXIII), m. p. 191° (25%) (cf. D). *1-Methyl-5 : 5-pentamethylene-2-thiohydantoin* (VIII) gave *1 : 3-dimethyl-5 : 5-pentamethylene-2-thiohydantoin* (XI), colourless jagged needles (from aqueous methanol), m. p. 118—119° (70%) (Found: C, 56·4; H, 7·5; N, 13·0. $C_{10}H_{16}ON_2S$ requires C, 56·6; H, 7·55; N, 13·2%); light

absorption: Maxima, 2380 and 2650 A., ε = 13,570 and 17,100 respectively. **5 : 5-Pentamethylene-2 : 4-dithiohydantoin** (XII) gave a mixture of products. These separated from the reaction mixture *2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XIV), colourless needles (from methanol), m. p. 217—218° (26%) (Found: C, 50·7; H, 6·6; N, 12·7. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption: Maximum, 2820 A.; ε = 11,600. Inflexion, 3070 A., ε = 8,700. The residue, after removal of ether and excess of diazomethane, was triturated with light petroleum (b. p. 40—60°) to give *3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XV), m. p. 191—192° (46%) (cf. E). The light-petroleum washings, on evaporation, left an oil which was not purified but on acid hydrolysis lost methanethiol and gave *3-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXIII), m. p. 191° (9%) (cf. D); this indicated the presence of *4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XX). Methylation of *1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XIII) with diazomethane gave **1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin** (XVII), m. p. 126° (45%) (cf. E), and *2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XVIII), m. p. 148—149° (5%) (cf. A). *3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XV) gave *4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XX), m. p. 63—64° (90%) (cf. A).

(C) *Methylations with Methyl Sulphate.*—**5 : 5-Diphenyl-2 : 4-dithiohydantoin** (XII) (15 g.) was dissolved in dilute aqueous sodium hydroxide (165 c.c.; 4%). To the stirred solution, methyl sulphate (9 g.) was added during 10 minutes, the temperature being kept below 20°. The mixture was stirred for a further 2 hours and was then filtered. The solid product, recrystallised from methanol, gave *2 : 4-dimethylthio-5 : 5-diphenylglyoxaline* (XXI), m. p. 140° (25%) (cf. A). The alkaline filtrate was clarified with kieselguhr and then acidified with hydrochloric acid, and the product was extracted with chloroform. The dried chloroform solution was passed through an alumina column, affording *2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XIV), m. p. 256° (19%) (cf. A), and *4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline* (XVI), bright orange-yellow needles (from methanol), m. p. 211° (13%) (Found: C, 64·3; H, 4·65; N, 9·1. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), which darkened on exposure to light.

In a similar manner **5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin** (XIII) gave a mixture from which there were obtained, by chromatographic separation from ether–chloroform (1 : 1) on alumina, *5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin* (XVII), m. p. 167° (12%) (cf. E), and *2-thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XVIII), m. p. 205° (30%) (cf. A).

Methyl sulphate (32 g.) was added during 5 minutes to a stirred solution of **5 : 5-pentamethylenehydantoin** (I) (34 g.) in aqueous sodium hydroxide (10 g. in 200 c.c.), the temperature being kept below 40°. After being stirred for a further 10 minutes the mixture was cooled and filtered, and the solid product was recrystallised from methanol, giving *3-methyl-5 : 5-pentamethylenehydantoin* (III), colourless needles, m. p. 212—213° (75%) (Found: C, 59·5; H, 7·8; N, 15·3. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7; N, 15·4%).

Similarly *1-methyl-5 : 5-pentamethylenehydantoin* gave **1 : 3-*dimethyl*-5 : 5-*pentamethylenehydantoin***, colourless prisms (from aqueous methanol), m. p. 68—69° (74%) (Found: C, 60·8; H, 8·2; N, 14·4. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2; N, 14·3%).

5 : 5-Pentamethylene-2 : 4-dithiohydantoin (XII) (48 g.) in aqueous sodium hydroxide (360 c.c.; 8%) was methylated by addition of methyl sulphate (36 g.) with stirring, during 20 minutes, temperature being kept at 5—10°. The mixture was stirred for a further 3 hours, the temperature being allowed to rise to 20°. The insoluble solid was filtered off and recrystallised from aqueous methanol, to give *2 : 4-dimethylthio-5 : 5-pentamethyleneglyoxaline* (XXI) as colourless needles, m. p. 48—49° (33%) (Found: C, 53·0; H, 7·1; N, 12·5. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maximum, 2570 A.; ε = 6,800. This substance was soluble in dilute hydrochloric acid and could be distilled *in vacuo* (b. p. 120°/0·3 mm.). The crude alkali-insoluble solid also appeared to contain some *4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XX), for acid hydrolysis gave, in addition to *5 : 5-pentamethylenehydantoin* (I), an alkali-insoluble product identified as *3-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXIII), m. p. 191° (cf. D). The alkaline filtrate from the methylation was acidified below 10° with phosphoric acid, and the solid was filtered off, washed with water, and dried. Chromatographic separation from chloroform solution on alumina gave as the main product *4-thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XVI), bright yellow needles (from aqueous methanol), m. p. 161° (30%) (Found: C, 50·6; H, 6·6; N, 13·4. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption: Maxima, 2550, 2970, and 3300 A.; ε = 7,850, 8,340, and 8,890 respectively. This compound darkened on exposure to light. It was accompanied by small quantities of *3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XV), m. p. 191—192° (cf. E), and *2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XIV), m. p. 217—218° (cf. B).

1-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII), methylated under similar conditions, gave a mixture which was separated chromatographically from chloroform solution on alumina into **1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin** (XVII), m. p. 126° (29%) (cf. E), and *2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XVIII), m. p. 148—149° (23%) (cf. A).

(D) *Hydrolysis of Methylthio-compounds.*—The methylthio-compound (5 g.) in 20% hydrochloric acid (20 c.c.) was heated under reflux for ½—4 hours. Methanethiol was evolved, and on cooling the product separated. In the *5 : 5-diphenyl* series, where the starting materials were sparingly soluble, the hydrolysis was usually carried out in a mixture of 36% hydrochloric acid (20 c.c.) and ethanol (50 c.c.).

In this way *2 : 4-dimethylthio-5 : 5-diphenylglyoxaline* (XXI) gave **5 : 5-diphenylhydantoin (I)**, colourless crystals (from aqueous methanol), m. p. 300° (60%). The same product was obtained from *2-keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XXIV) (65%). *2-Keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XXVII) gave *5 : 5-diphenyl-1-methylhydantoin* (II), long colourless prisms (from aqueous methanol), m. p. 225° (94%) (Found: C, 72·3; H, 5·3; N, 11·2. Calc. for $C_{16}H_{14}O_2N_2$: C, 72·2; H, 5·25; N, 11·5%). The same product was obtained in almost theoretical yield from *4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline* (X). *4-Keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline* (IX) gave *5 : 5-diphenyl-3-methylhydantoin* (III)

in almost theoretical yield. **4-Thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline** (XVI) gave *5 : 5-diphenyl-4-thiohydantoin* (XXII), bright yellow prisms (from methanol), m. p. 273—274° (80%) (Found : C, 66·8; H, 4·6; N, 10·4. $C_{15}H_{12}ON_2S$ requires C, 67·2; H, 4·5; N, 10·45%). **2-Thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline** (XVIII) gave *5 : 5-diphenyl-1-methyl-2-thiohydantoin* (VIII), cream needles (from aqueous ethanol), m. p. 218° (83%) (Found : C, 68·2; H, 4·95; N, 10·0. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%). **4-Thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline** (XX) gave *5 : 5-diphenyl-3-methyl-4-thiohydantoin* (XXIII), pale yellow needles (from aqueous methanol), m. p. 202° (82%) (Found : C, 68·2; H, 5·1; N, 9·95. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%).

2 : 4-Dimethylthio-5 : 5-pentamethyleneglyoxaline (XXI), **4-keto-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline** (VI), or **2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline** (XXIV) gave *5 : 5-pentamethylenehydantoin* (I), m. p. 217—218°, on acid hydrolysis. **4-Keto-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline** (IX) gave *3-methyl-5 : 5-pentamethylenehydantoin* (III), m. p. 212° (47%). **2-Thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline** (XIV) gave *5 : 5-pentamethylene-2-thiohydantoin* (V), m. p. 190—191° (81%); light absorption : Maxima, 2240 and 2660 A.; $\varepsilon = 9{,}910$ and 20,300 respectively. **4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline** (XVI) gave *5 : 5-pentamethylene-4-thiohydantoin* (XXII), m. p. 240°; light absorption : Maxima, 2300 and 2780 A.; $\varepsilon = 4{,}360$ and 15,500 respectively. **4-Thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline** (XX) gave *3-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXII), almost colourless plates (from methanol), m. p. 190—191° (71%) (Found : C, 54·8; H, 6·9; N, 14·1. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption : Maxima, 2290 and 2780 A.; $\varepsilon = 5{,}300$ and 15,100 respectively. **2-Thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline** (XVIII) gave in almost quantitative yield *1-methyl-5 : 5-pentamethylene-2-thiohydantoin* (VIII), colourless needles (from aqueous methanol), m. p. 153° (Found : C, 54·8; H, 7·2; N, 14·1. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption : Maxima, 2300 and 2650 A.; $\varepsilon = 7{,}450$ and 12,750 respectively.

2 : 4-Dimethylthio-5 : 5-diphenylglyoxaline (XXI) (8 g.) was heated under reflux for ½ hour with glacial acetic acid (80 c.c.) and water (20 c.c.). Methanethiol was evolved. Water (200 c.c.) was added, the mixture was cooled, and the product was filtered off, washed with water, and recrystallised from ethanol, to give *2-keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XXIV), colourless prisms, m. p. 264° (64%) (Found : C, 67·7; H, 5·0; N, 9·5. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%).

(E) *Introduction of Sulphur.*—The hydantoin (10 g.) and phosphorus pentasulphide (10 g.) were suspended in tetralin (60 c.c.; more was occasionally required with sparingly soluble compounds), and boiled under reflux with efficient stirring for 1—1½ hours. The mixture was filtered hot. The product separated from the solution on cooling. It was filtered off, and purified by recrystallisation.

5 : 5-Diphenyl-2-thiohydantoin (V) gave *5 : 5-diphenyl-2 : 4-dithiohydantoin* (XII), bright yellow prisms (from methanol), m. p. 268° (70%), also produced similarly from **4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline** (VI). *5 : 5-Diphenyl-1-methylhydantoin* (II) gave *5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin* (XIII), lemon-yellow prisms (from methanol), m. p. 217° (82%) (Found : C, 64·8; H, 4·85; N, 9·25. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), also obtained from 2-keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XXVII). *5 : 5-Diphenyl-3-methylhydantoin* (III) gave *5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin* (XV), yellow prisms (from methanol), m. p. 206° (47%) (Found : C, 64·6; H, 4·75; N, 9·3. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%). *5 : 5-Diphenyl-1 : 3-dimethylhydantoin* (IV) gave *5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin* (XVII), yellow needles (from methanol), m. p. 167° (60%) (Found : C, 65·5; H, 5·3; N, 8·8. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%).

1-Methyl-5 : 5-pentamethylenehydantoin (II) gave *1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XIII), yellow hexagonal plates (from aqueous methanol), m. p. 192—193° (60%) (Found : C, 50·2; H, 6·5; N, 13·25. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption : Maxima, 2250 and 2980 A.; $\varepsilon = 7{,}430$ and 26,200. *3-Methyl-5 : 5-pentamethylenehydantoin* (III) gave *3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XV), yellow prisms (from methanol), m. p. 191—192° (46%) (Found : C, 50·5; H, 6·8; N, 13·4. $C_{10}H_{16}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption : Maxima, 2250 and 2980 A.; $\varepsilon = 6{,}690$ and 29,100 respectively. This compound was also obtained similarly from *3-methyl-5 : 5-pentamethylene-2-thiohydantoin* (VII). *1 : 3-Dimethyl-5 : 5-pentamethylenehydantoin* (IV) gave *1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin* (XVII), long yellow needles (from ethanol), m. p. 126° (26%) (Found : C, 52·5; H, 7·2; N, 12·0. $C_{12}H_{18}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption : Maxima, 2240 and 2980 A.; $\varepsilon = 6{,}300$ and 26,250 respectively.

(F) *2-Aminoethanol Derivatives.*—*5 : 5-Diphenyl-2 : 4-dithiohydantoin* (XII) was boiled under reflux for ½ hour with 5 parts of 2-aminoethanol. Hydrogen sulphide was evolved, and after cooling the solid product was filtered off. Recrystallisation from ethanol gave *4-2′-hydroxyethylimino-5 : 5-diphenyl-2-thiohydantoin*, colourless crystals, m. p. 218° (60%) (Found : C, 63·8; H, 5·6; N, 13·0. $C_{17}H_{17}ON_3S,\frac{1}{2}H_2O$ requires C, 63·8; H, 5·95; N, 13·1%), obtained also from *2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XIV). In a similar manner *5 : 5-diphenyl-2-thiohydantoin* (V), on refluxing for 3 hours with aqueous 2-aminoethanol, gave *2-2′-hydroxyethylimino-5 : 5-diphenylhydantoin*, colourless prisms (from dimethylformamide), m. p. 298° (Found : C, 68·9; H, 5·9; N, 14·3. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·75; N, 14·25%), also was obtained by the action of 2-aminoethanol on *4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline* (VI). **4-Thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline** (XVI) with aqueous 2-aminoethanol (15 minutes under reflux) gave *2-2′-hydroxyethylimino-5 : 5-diphenyl-4-thiohydantoin*, colourless crystals (from aqueous ethanol), m. p. 239° (Found : C, 66·0; H, 5·0; N, 13·3. $C_{17}H_{17}ON_3S$ requires C, 65·6; H, 5·45; N, 13·5%). **2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline** (XXIV), on heating under reflux with aqueous 2-aminoethanol for 15 minutes, gave an almost quantitative yield of *4-2′-hydroxyethylimino-5 : 5-diphenylhydantoin*, colourless crystals (from ethanol), m. p. 249° (Found : C, 69·2; H, 5·7; N, 14·1. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·75; N, 14·25%). *5 : 5-Diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin* (XVII), when

heated under reflux with aqueous 2-aminoethanol for 4 hours, gave *4-2′-hydroxyethylimino-5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin*, colourless crystals (from aqueous ethanol), m. p. 158° (Found : C, 67·2; H, 6·2; N, 12·2. $C_{19}H_{21}ON_3S$ requires C, 67·2; H, 6·2; N, 12·4%). It was found difficult to complete this reaction, and in the isolation of the product it was best to extract it with excess of cold dilute hydrochloric acid, filter from unchanged starting material, and reprecipitate it with ammonia before crystallisation. This compound, on being heated under reflux for ½ hour with 50 parts of 20% hydrochloric acid, was hydrolysed to 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI), colourless needles (from aqueous methanol), m. p. 144° (Found : C, 68·8; H, 5·3; N, 9·7. Calc. for $C_{17}H_{16}ON_2S$: C, 68·9; H, 5·4; N, 9·5%).

4-2′-Hydroxyethylimino-1-methyl-5 : 5-pentamethylene-2-thiohydantoin was obtained in 55% yield by heating 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII) with aqueous 2-aminoethanol. The oily product solidified on cooling and trituration with ether, and crystallised from methanol–ether in colourless prisms, melting incompletely at 153—159° and clearing at 174—175° (Found, on material dried *in vacuo* at 56° : N, 15·5; on material dried *in vacuo* at 140° for 4 hours : N, 17·8. $C_{11}H_{18}ON_2S,2H_2O$ requires N, 15·2%; $C_{11}H_{18}ON_2S$ requires N, 17·4%). The same compound was obtained in quantitative yield by heating 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII) (1·15 g.) with 2-aminoethanol (0·6 g.) at 110—120° for 15 minutes. Hydrolysis of this compound with boiling 20% hydrochloric acid gave, in 91% yield, 1-methyl-5 : 5-pentamethylene-2-thiohydantoin (VIII), colourless needles (from aqueous methanol), m. p. 153° (cf. D). 4-2′-Hydroxyethylimino-5 : 5-pentamethylene-2-thiohydantoin, m. p. 245°, 4-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 255° (decomp.), and 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°, were prepared by the action of 2-aminoethanol on the corresponding methylthio-derivatives, and were identical with the products described in Part II. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI), with 2-aminoethanol at 110—120° for 10 minutes, gave *2-2′-hydroxyethylimino-5 : 5-pentamethylene-4-thiohydantoin*, colourless prisms (from methanol), m. p. 193—194° (Found : C, 52·6; H, 7·3; N, 18·3. $C_{10}H_{17}ON_3S$ requires C, 52·9; H, 7·5; N, 18·5%). This compound, on treatment with methyl iodide and methanolic sodium hydroxide as described in A, gave an oil (91%), which was not analysed but apparently consisted in the main of 4-methylthio-2-2′-hydroxyethylimino-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline, since on acid hydrolysis it lost methanethiol and gave 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°, identical with that described above and in Part II. The oily methylthio-derivative was heated with 2-aminoethanol at 130—140° for ½ hour. Methanethiol was evolved and the product was a water-soluble glass, which crystallised from methanol–ether to give *2 : 4-di-(2′-hydroxyethylimino)-5 : 5-pentamethylenehydantoin*, small colourless prisms, m. p. 117—118° (Found : N, 21·5. $C_{15}H_{25}O_3N_5$ requires N, 22·0%). This product, too, was hydrolysed by acid to 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°.

(G) *Miscellaneous.—α-Methylaminodiphenylacetamide.* α-Chlorodiphenylacetamide (5 g.) (Steinkopf, *loc. cit.*) was heated in a sealed tube at 80—90° for 20 hours with a saturated solution of methylamine in benzene (50 c.c.). The contents of the tube were filtered from methylamine hydrochloride, evaporated to dryness, and recrystallised from methanol to give *α-methylaminodiphenylacetamide*, m. p. 191° (2·7 g., 55%) (Found : N, 11·3. $C_{15}H_{16}ON_2$ requires N, 11·65%). This was recovered unchanged after being heated with carbon disulphide in ethanol in a sealed tube at 80—90° for 20 hours.

5 : 5-Diphenyl-3-benzylhydantoin.—To a solution of 5 : 5-diphenylhydantoin (6 g.) in ethanol (50 c.c.) were added benzyl chloride (3 g.) and a solution of sodium hydroxide in the minimum of water. The mixture was heated under reflux for 17 hours and was poured into water. The solid product was filtered off and recrystallised from methanol to give *5 : 5-diphenyl-3-benzylhydantoin*, m. p. 151° (5·7 g., 70%) (Found : N, 7·9. $C_{22}H_{18}O_2N_2$ requires N, 8·2%).

5 : 5-Diphenyl-3-benzyl-1-methylhydantoin.—To a solution of 5 : 5-diphenyl-3-benzylhydantoin (3·4 g.) in ethanol (50 c.c.) were added 20% aqueous sodium hydroxide (2 c.c.) and methyl sulphate (1·3 g.). The mixture was heated under reflux for 4 hours, cooled, and filtered. The filtrate was poured into water, and the oil which separated crystallised on storage. Recrystallisation from methanol gave *5 : 5-diphenyl-3-benzyl-1-methylhydantoin*, m. p. 125° (1·5 g., 42%) (Found : N, 8·1. $C_{23}H_{20}O_2N_2$ requires N, 7·9%). Attempts to debenzylate this compound by hydrogenation in methanol solution using a palladium–charcoal catalyst at 100° were unsuccessful; the starting material was recovered unchanged.

1-Methyl-5 : 5-pentamethylenehydantoin.—α-Methylaminohexahydrobenzonitrile (42 g.) was suspended in water (100 c.c.) and neutralised by the addition of 36% hydrochloric acid. A solution of potassium cyanate (27 g. in 50 c.c. water) was added at 30—35° with stirring, and the mixture was stirred for a further ½ hour. The *ureide* separated as an oil which crystallised, and was filtered off. A sample, recrystallised from methanol in colourless needles, had m. p. 167—168° (Found : C, 59·9; H, 8·0; N, 23·0. $C_9H_{14}ON_2$ requires C, 59·7; H, 8·3; N, 23·2%). It was suspended in water (100 c.c.) with stirring, and 36% hydrochloric acid (40 c.c.) was added. The solid went into solution and the product separated. The mixture was heated to 80—90° on the steam-bath for 15 minutes to complete the reaction, and then cooled, and the *product* (II) filtered off, washed with cold water, and recrystallised from hot water as long needles, m. p. 174° (20 g., 36%) (Found : C, 59·5; H, 7·6; N, 15·0. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7; N, 15·4%).

5 : 5-Pentamethylene-2 : 4-dithiohydantoin.—The light absorption of this compound (XII) showed maxima at 2270 and 2970 A., and ε = 5,540 and 26,300 respectively.

The authors express their thanks to Dr. F. R. Cropper for the light-absorption measurements, and to Mr. G. Bratt and Miss M. Smith for invaluable technical assistance. Microanalyses were carried out by Messrs. Weiler and Strauss, Oxford.

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80. *Hydroaromatic Steroid Hormones. Part I.* 10-*Nortestosterone.*

By Arthur J. Birch.

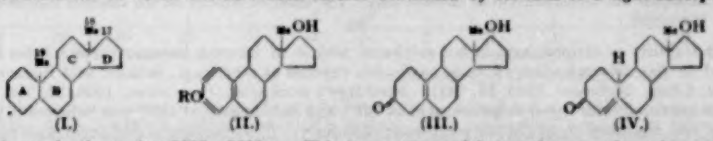
The problem of making physiologically active hormone substitutes is discussed, and the preparation of 10-nortestosterone (IV) is described.

One of the chief difficulties associated with the synthesis of steroid hormones is the quaternary nature of the carbon atoms which carry the angular methyl groups. This difficulty has contributed to prevent the synthesis of the non-aromatic hormones containing two such groups, and there is no known method of introducing the 19-Me (cf. I) into the synthetic aromatic hormones such as (+)-œstrone (ring A aromatic) to produce hydroaromatic compounds convertible into non-aromatic hormones such as testosterone. The only successful attempt on a model substance is that of Woodward (*J. Amer. Chem. Soc.*, 1940, **62**, 1208), but the reaction apparently failed with œstrone.

With the increasing importance of steroid hormones, it seems necessary to examine more closely the structural requirements for physiological activity, in particular whether this is retained by compounds lacking the angular methyl groups and therefore available by the reduction of aromatic systems. Œstrogenic activity is comparatively unspecific and is shown by compounds differing greatly in structure from the natural hormones, but for the androgenic, progestational, and cortical hormones even slight changes in the space-distribution of groups are sufficient to depress or abolish activity. Evidence is, however, available in several cases that the 19-Me (between rings A and B) is not absolutely essential for activity. Dirscherl, Kraus, and Voss (*Z. physiol. Chem.*, 1936, **241**, 1; cf. Schering-Kahlbaum A.-G., B.P. 423,287/1935) reported the reduction of (+)-œstrone to an octahydro-derivative (ring A fully reduced and hydroxyl in the 17-position) which is androgenic, and must be considered as the first synthetic compound with this activity; and Ehrenstein (*J. Org. Chem.*, 1944, **9**, 435) obtained a 19-norprogesterone which is claimed to be as active as progesterone itself. He also prepared a 19-nordeoxycorticosterone, which is, however, inactive. Neither of these last two products could be crystallised and they are probably mixtures of isomers.

The 18-Me (between rings C and D) appears to be essential for high activity, at least with the œstrogenic hormones equilenin and œstrone, but this effect may be due merely to the fact that it prevents the (natural) *trans*-junction of rings C and D from assuming the more stable *cis*-configuration. The methyl group can be replaced by ethyl or *n*-propyl without great diminution in activity (Bachmann and Holmes, *J. Amer. Chem. Soc.*, 1940, **62**, 2750). With two fused six-membered rings, the *trans*-junction is the more stable, and it is known that if ring D of the natural hormones is converted into a six-membered ring the compounds obtained are highly active (Goldberg and Wyndler, *Helv. Chim. Acta*, 1943, **26**, 1142; Goldberg and Studer, *ibid.*, 1941, **24**, 478), so it may be possible to omit the 18-Me in such cases.

The synthetic approach to nor-steroid hormones has now been greatly simplified by Birch and Mukherji's method of reduction (*Nature*, 1949, **163**, 766; *J.*, 1949, 2351), by which an aryl glyceryl or an aryl 2-hydroxyethyl ether is reduced with sodium and an alcohol in liquid ammonia, and the dihydro-derivative so obtained hydrolysed to an unsaturated ketone. "α"-Œstradiol 1'-glycerol ether [II; R = CH_2·$CH(OH)$·CH_2·OH] was thus reduced to (III), the constitution of which has now been further confirmed by its lack of a light-absorption



(I.) (II.) (III.) (IV.)

maximum in the region 2200—3000 A. This βγ-unsaturated ketone has now been isomerised by ethanolic sodium ethoxide to the αβ-unsaturated ketone (IV), which is a 10-*nortestosterone*. Although two stereoisomers are to be expected from the isomerisation, only one crystalline product (orientation at $C_{(10)}$–H unknown) could be isolated (in 60% yield), the remainder being a gum. The constitution assigned to the compound is confirmed by its light absorption in ethanol, with a maximum at 2400—2415 A., $\varepsilon_{max.}$ 17,000, and a low-intensity band at 3075 A., $\varepsilon_{max.}$ 92·5. Dannenberg (*Abhandl. preuss. Akad. Wiss.*, 1939, **21**, 3) gives for testosterone in ethanol a band at 2410 A., log $\varepsilon_{max.}$ 4·20.

The advantages of the reduction method are that ring A can be kept aromatic up to the last

stages, thus simplifying synthetic reactions on the other parts of the molecule; and that a *cyclo*hexenone ring is produced which is characteristic of hormones such as testosterone, progesterone, cortisone, and corticosterone. It is possible in many cases to protect groups such as carbonyl during the reduction (Birch, unpublished work).

This work is being pursued with the object of making further hormone analogues from (+)-œstrone in order to see whether the expenditure of effort necessary for the complete synthesis of such nor-steroids is likely to be justified.

Experimental.

10-*Nortestosterone* (IV).—The following method is somewhat better than that already given (Birch and Mukherji, *loc. cit.*) for the preparation of (III). " α "-Œstradiol 1'-glycerol ether (980 mg.) was dissolved in warm ethanol (30 c.c.) and stirred into liquid ammonia (300 c.c.). Potassium (3 g.) was rapidly added in small pieces with stirring and, after the reaction was complete, water (75 c.c.) was used to decompose the mixture. The ammonia was rapidly evaporated, finally under reduced pressure, and the solution just neutralised by the addition of hydrochloric acid, followed by sufficient acid to give a 5%-acid solution. This solution, containing a suspension, was then shaken with ethyl acetate (30 c.c.), which eventually dissolved the gummy solid as hydrolysis proceeded. The ethyl acetate solution was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was taken up in ethyl acetate (5 c.c.) and chromatographed on alumina (cf. Birch and Mukherji, *loc. cit.*) in the same solvent. The eluate was divided arbitrarily into fractions until evaporation under reduced pressure gave a non-crystallisable gum instead of a solid. The collected solid recrystallised from ethyl acetate as large flat prisms (215 mg.), m. p. 187—188°, $\lambda_{max.}$ 2720—2940 A., $\varepsilon_{max.}$ 51·4 (ethanol). This compound (III) (200 mg.) was dissolved in warm ethanol (10 c.c.) and added to a solution of sodium (15 mg.) in ethanol (4 c.c.). The mixture was kept at 50° for 5 minutes under nitrogen. After acidification with a few drops of acetic acid the solvent was removed under reduced pressure, and the residue washed with water, taken up in ethyl acetate (5 c.c.), and chromatographed on alumina (cf. Birch and Mukherji, *loc. cit.*) in the same solvent. The first fractions crystallised on removal of the solvent, and 10-*nortestosterone* (IV) was crystallised from light petroleum (b. p. 60—80°) containing a few drops of ethyl acetate, as large colourless prisms (120 mg.), m. p. 111°; $\lambda_{max.}$ 2400—2415 A., $\varepsilon_{max.}$ 17,000; $\lambda_{max.}$ 3075 A., $\varepsilon_{max.}$ 92·5 (ethanol) (Found: C, 78·5; H, 9·3. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%).

This work was carried out during the tenure of the Smithson Research Fellowship of the Royal Society. The author is grateful to Professor Sir Robert Robinson, P.R.S., for a gift of (+)-œstrone, to Professor A. R. Todd, F.R.S., for the hospitality of his laboratory, and to Dr. R. N. Haszeldine for the absorption spectra.

The University Chemical Laboratory, Cambridge. [*Received, October 25th*, 1949.]

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81. *Decomposition of Chromic Acid in Sulphuric Acid. The First-order Thermal Reaction.*

By Ernest E. Aynsley.

The thermal decomposition of chromic acid in sulphuric acid between 140° and 170° has been studied. In concentrated solution the reaction is complex, but in 81·5% sulphuric acid and with concentrations of solute <0·05*M*. a reaction of first order with respect to chromic acid occurs with an activation energy of 10·3 ± 0·5 kcals. At high acid concentrations chromic sulphate inhibits the decomposition, but its effect decreases as the sulphuric acid concentration falls and disappears in about 82% sulphuric acid. In more dilute acid chromic sulphate slightly catalyses the decomposition of chromic acid. The effect of stirring on the reaction has been examined.

The stability of chromic acid in hot sulphuric acid is of interest because these solutions are used in the determination of such oxidisable vapours as ether (*e.g.*, Schaffer and Ronzoni, *J. Biol. Chem., Baltimore*, 1923, **57**, 741). Snethlage's work (*Rec. Trav. chim.*, 1936, **55**, 712, 874) with unstirred (*vide infra*) sulphuric acid at 138°, and fuming acid at 100°, was believed to show that two reactions occur (in the main simultaneously): (i) a reaction of first order with respect to chromic acid, with a velocity coefficient rising with increasing sulphuric acid concentration up to 99% and thereafter much more rapidly, and (ii) a reaction of second order with respect to chromic acid, with a velocity coefficient rising with the sulphuric acid content up to a concentration of 81% and then falling as the concentration rose to 99%. Chromic sulphate, prepared by reducing chromic acid in sulphuric acid with mannitol or salicylic acid, was found to catalyse the decomposition of chromic acid, the effect decreasing as the concentration of the sulphuric acid was increased and becoming negative in sulphuric acid stronger than 95%.

The speed of decomposition at 138°, even in the most favourable concentrations of acid is not high. Snethlage followed the quickest reaction only to 50% and the slower reactions to less

than about 15%. In the present work, with 0·010—0·702N-chromic acid, higher temperatures (140—170°) were employed, thus enabling the reaction to be followed nearly to completion.

Experimental.

Solutions were prepared by shaking the solid with sulphuric acid, setting the mixtures aside for 24 hours, and filtering them through sintered glass. 25-Ml. portions were heated in a 100-ml., Hysil, round-bottomed flask closed with a hollow stopper carrying a 6" glass stem through which passed a glass stirrer. Precaution was taken to prevent access of dust or other contaminants, and it was shown that there was no appreciable change in the moisture content during the heating which was by a large bath of liquid paraffin maintained within ±0·2° of the desired temperature. For a determination the flask was cooled in boiling water, followed by cold water, and its contents washed into excess of water and titrated with standard ferrous and permanganate solutions.

Table I establishes that equivalent solutions of potassium dichromate, ammonium dichromate, and chromic acid in sulphuric acid behave identically, presumably as a complex involving chromic acid, and since pure potassium dichromate is readily available it was used throughout. Potassium sulphate is without measurable influence: an excess of 50 molecular parts increased the hourly decomposition of 0·06N-potassium dichromate in 99·05% sulphuric acid by only 1·6%.

Table I.

Percentage losses in one hour in 99·15% H_2SO_4 *at* 160°.

Normality of solution.	$K_2Cr_2O_7$.	$(NH_4)_2Cr_2O_7$.	CrO_3.
0·010	18·0	17·8	17·9
0·025	17·7	17·9	18·1
0·100	17·9	18·0	18·3
0·150	17·5	18·2	18·5
0·250	18·0	18·5	18·8
0·400	18·6	18·9	19·1

An effect on the course of the reaction which has not previously been observed is that of stirring. In solutions of lower concentrations the rate of decomposition may be increased as much as 27% by this

Fig. 1.

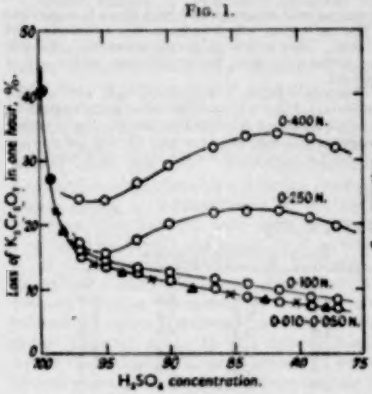
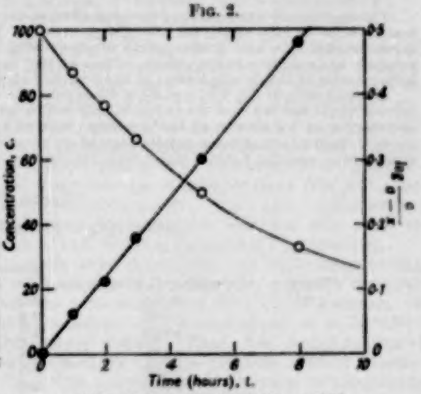


Fig. 2.



0·05N-CrO_3 *in* 81·5% H_2SO_4 *at* 170°.

means, but in concentrated solutions (about 0·7N.) the rates in stirred and in unstirred solutions are identical. Both conditions yielded reproducible results. Since precautions were always taken to see that a solution was at the required temperature before timing a run, the difference cannot be a result of the unstirred mixtures not being at the temperatures of the paraffin bath, the low thermal conductivity, or the lack of convection in the system. The acceleration is not affected by oxygen because, when the solution is agitated by a stream of preheated oxygen, admittedly less effectively than by the stirrer, a 20·1% increase was recorded in a 0·15N-solution of potassium dichromate in 90% sulphuric acid. This suggests that the reaction is not reversed by molecular oxygen. Nor was it due to increased contact with the surface since a 20-fold increase in the glass surface was without influence on the reaction, which is presumed homogeneous. Snethlage used unstirred solutions; the results reported in this work were obtained in stirred solutions.

Figure 1 shows the initial percentage losses, per hour, of chromic acid in sulphuric acid of different strengths at 160°, for six concentrations of solute. Clearly in more concentrated solutions of chromic acid the reaction is complex and reaches a maximum speed in 81·5% sulphuric acid. At a solute

concentration of <0·1N., the initial speed falls steadily with decreasing sulphuric acid concentration and at concentrations less than 0·05N. the initial percentage losses per hour are almost identical in all acid concentrations. In acid solutions stronger than 99% there is a rapid increase in speed and the initial percentage losses are identical for all concentrations of solute. However, in fuming acid the decomposition is so rapid that accurate measurement is difficult.

Table II shows that in 99·15% sulphuric acid at 160° there is a fall in the reaction rate as the heating proceeds, shown by the decreasing values of k calculated from the first-order equation $k = (2{\cdot}303/t) \log_{10} 100/(100 - x)$ (t = time of heating in seconds, and x = the percentage loss of chromic acid in time t).

TABLE II.

Heating periods (160°) in hours. Values of $k \times 10^4$. 99·15% H_2SO_4.

Normality.	1 hr.	2 hr.	4 hr.	8 hr.	16 hr.	Normality.	1 hr.	2 hr.	4 hr.	8 hr.	16 hr.
0·025	5·41	4·96	3·95	3·51	2·98	0·150	5·28	4·53	3·63	3·15	2·84
0·050	5·51	4·80	3·78	3·46	—	0·400	5·72	4·86	4·17	3·47	—
0·075	5·44	4·70	3·72	3·23	—	0·702	6·24	5·67	4·86	4·32	—
0·100	5·48	4·45	3·56	3·13	—						

This fall in speed is due to chromic sulphate which is a by-product of the reaction, and comparable results can be obtained by using added chromic sulphate. Table III gives (*a*) the percentage losses observed in the first hour at 160° in a 0·025N-chromic acid solution in 99·15% sulphuric acid to which different amounts of chromic sulphate (prepared by reducing chromic—sulphuric acid solutions with sulphur dioxide) were added and, for comparison, (*b*) the calculated percentage losses in solutions containing the decomposition product $Cr_2(SO_4)_3$ equal in concentration to that added in (*a*).

TABLE III.

r = ratio $Cr_2(SO_4)_3/CrO_3$. 0·025N-CrO_3 in 99·15% H_2SO_4 at 160°.

$r = 0$.	$r = 0{\cdot}5$.		$r = 0{\cdot}6$.		$r = 0{\cdot}8$.		$r = 1{\cdot}0$.		$r = 2{\cdot}3$.	
	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)
17·7	13·9	13·0	12·6	12·0	9·7	9·4	9·3	9·2	9·1	9·0

The results indicate that the poisoning effect is due to chromic sulphate and that there is a concentration limit to this effect, *viz.*, $1Cr_2(SO_4)_3 : 1CrO_3$. The poisoning effect falls as the sulphuric acid concentration falls and it disappears in about 82% acid. Below this acid concentration, chromic sulphate has a slight catalytic effect. Thus, at 160° in a 0·06N-CrO_3–80% H_2SO_4 solution with $r = 4$, a 10% increase in the decomposition in one hour was observed.

Working with 81·5% acid and using concentrations of solute <0·05N. it was shown that within these narrow limits the reaction obeys reasonably well a kinetic equation of the first order with respect to dichromate, as is shown by (i) the constant values of k at all temperatures (Table IV), (ii) Fig. 2 which shows a typical set of these results plotted as (*a*) concentration against time and (*b*) log $[a/(a - x)]$ against time, and (iii) Table V which gives the times of one-fifth conversion for the same set of results.

TABLE IV.

Values of $k \times 10^4$ *in* 81·5% H_2SO_4.

Temp.	Normality of solution.	Heating periods in hours. 1.	2.	3.	5.	8.
170°	0·050	3·9	3·6	3·8	3·9	3·9
	0·025	3·8	3·7	3·7	3·6	3·7
	0·010	3·7	4·0	3·6	3·5	3·8
165	0·050	2·9	2·8	2·9	2·8	2·6
	0·025	2·8	2·8	3·0	2·9	2·7
	0·010	3·0	2·9	3·0	2·7	2·7
160	0·050	2·1	2·2	2·2	2·1	2·0
	0·025	2·3	2·3	2·3	2·0	2·1
	0·010	2·2	2·2	2·1	2·2	2·0
155	0·050	1·6	1·7	1·6	1·6	1·5
	0·025	1·7	1·6	1·5	1·7	1·6
	0·010	1·6	1·6	1·5	1·6	1·5
150	0·050	1·2	1·2	1·2	1·0	1·1
	0·025	1·1	1·3	1·2	1·3	1·2
	0·010	1·0	1·1	1·3	1·2	1·3

TABLE V.

Concn., %	100	80	60	50	40
$t_{\frac{1}{5}}$ (hours)	1·7	1·6	1·5	1·5	1·7

From these results the plots of $\log_{10} k$ against $1/T$ gives a straight line from which an Arrhenius activation energy of 10·3 ± 0·5 kcals. is obtained.

Analysis of the results shows that the thermal decomposition of chromic acid in sulphuric acid is complex in all solutions (except those within the narrow concentration limits of 81·5% sulphuric acid and solute concentration less than 0·05N. where a reaction of the first order prevails) and cannot be adequately accounted for by assuming a second-order reaction to be superimposed on a first-order reaction. Moreover, chromic sulphate is found to poison the reaction down to 82% sulphuric acid and thereafter to act as a mild catalyst. These results are not in agreement with those of Snethlage who found chromic sulphate to be a poison down to 95% H_2SO_4 and in more dilute sulphuric acid solutions to be a powerful catalyst.

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82. *Anhydrides of Polyhydric Alcohols. Part XIII. The Amino-derivatives of* 1 : 4-3 : 6-*Dianhydro-mannitol, -sorbitol, and* -L-*iditol, and their Behaviour towards Nitrous Acid.*

By V. G. BASHFORD and L. F. WIGGINS.

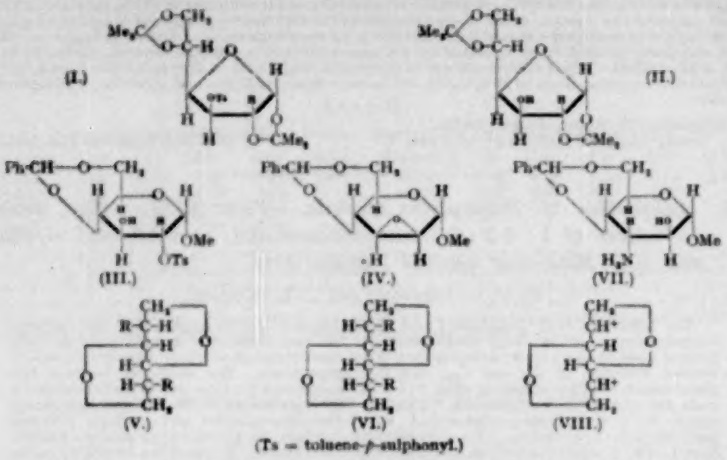
The behaviour of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-mannitol and -sorbitol towards nitrous acid has been investigated. It has been found that in both cases the only product isolated was 1 : 4-3 : 6-dianhydro-L-iditol, the formation of which must have involved Walden inversion at $C_{(2)}$ and $C_{(5)}$, and $C_{(3)}$, respectively. The similarity between this phenomenon and that occurring when 2 : 4-3 : 5-dimethylene D-gluco- and -D-manno-saccharic acids are epimerised is emphasised. Although the replacement of the toluene-*p*-sulphonyl groups in 2 : 5-ditoluene-*p*-sulphonyl 1 : 4-3 : 6-dianydro-mannitol and -sorbitol proceeds smoothly with the formation of the corresponding diamines, the attempt to prepare the diamine from 1 : 4-3 : 6-dianhydro-L-iditol by the same procedure failed; in this case a secondary amine was formed which on the basis of its physical and chemical properties and, as a result of scale-model studies, is tentatively allocated the structure, 2 : 5-*imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol*. Further work designed to confirm or reject this conjecture is in progress.

In view of the interesting facts that have come to light during study of the deamination of amino-derivatives of partly substituted sugar derivatives containing hydroxyl groups situated *trans* to the amino-groups (Wiggins, *Nature*, 1946, **157**, 300) it was held worth while to investigate the deamination of the diamino-derivatives of the 1 : 4-3 : 6-dianhydrides of the epimerically related hexitols, D-mannitol, D-sorbitol, and L-iditol in which no free hydroxyl groups exist. A preliminary account of this work has already appeared (Bashford and Wiggins, *Nature*, 1949, **164**, 573). The deamination of amino-sugars such as 4 : 6-benzylidene 3-amino-α-methyl-3-deoxyaltroside led to the formation of ethylene oxide anhydro-rings, this particular amine giving 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside. The same phenomenon has been observed not only with appropriate glycoside derivatives, but also with those of 1 : 6-anhydro-sugars and sugar alcohols (Bashford and Wiggins, forthcoming publication).

If 2 : 5-diamino-dianhydro-2 : 5-dideoxyhexitols were deaminated, no such anhydro-ring formation could take place. Deamination of these substances might be expected to occur without Walden inversion, by analogy with the behaviour, towards alkaline reagents, of toluene-*p*-sulphonyl derivatives of sugars which contain no free hydroxyl group, or no hydroxyl group situated *trans* to the toluene-*p*-sulphonyloxy residue. Thus, 3-toluene-*p*-sulphonyl 1 : 2-5 : 6-di*iso*propylidene glucose (I) was hydrolysed by alkaline reagents without Walden inversion, to give di*iso*propylidene glucose (II). This contrasts with behaviour of compounds such as 2-toluene-*p*-sulphonyl 4 : 6-benzylidene α-methylglucoside (III), the alkaline hydrolysis of which is accompanied by Walden inversion: for from (III), 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (IV) is formed.

Deamination of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (V; R = NH_2) and -sorbitol (VI; R = NH_2) might be expected to lead only to the parent hexitols, 1 : 4-3 : 6-dianhydro-mannitol, (V; R = OH) and -sorbitol (VI; R = OH) respectively, especially since deamination of 4 : 6-benzylidene 3-amino-α-methyl-3-deoxyaltroside (VII) follows the same course as alkaline hydrolysis of 2-toluene-*p*-sulphonyl 4 : 6-benzylidene α-methylglucoside and gives rise to 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (IV). When, however, 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol was treated with sodium nitrite in acid solution and the liquid product treated with methanesulphonyl chloride, the dimethanesulphonate, m. p. 156°, of 1 : 4-3 : 6-dianhydro-L-iditol (Wiggins, *J.*, 1948, 1403) was obtained. This product was also isolated after similar treatment of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-

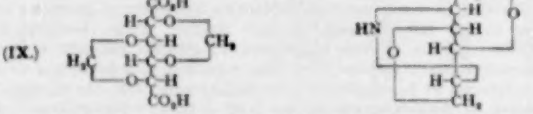
dideoxysorbitol. Although in neither case was any other dianhydrohexitol derivative isolated, the small yield of the L-iditol derivative indicated that it was not the only product. The fact that



(Ts = toluene-*p*-sulphonyl.)

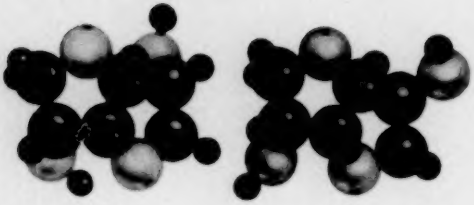
an L-iditol derivative has been obtained from both diamino-dianhydrodideoxyhexitols means that the deamination has been accompanied by Walden inversion, in the case of sorbitol at $C_{(5)}$, and in that of mannitol at both $C_{(3)}$ and $C_{(5)}$. This is explicable since deamination must involve the transitory formation of the carbonium cation (VIII) and this, on hydroxylation may take up the configuration of D-mannitol, D-sorbitol, or L-iditol. That in fact it takes up that of L-iditol to the apparent exclusion of the other two seems to indicate a configurational stability peculiar to this hexitol. The behaviour of the diamino-dianhydrohexitols towards deamination is in marked contrast to the alkaline hydrolysis of 3-toluene-*p*-sulphonyl di*iso*propylidene glucose, where Walden inversion, although possible because of the likelihood of the transitory formation of a carbonium cation (at $C_{(3)}$), does not take place.

This conversion of dianhydro-mannitol and -sorbitol into the corresponding derivative of L-iditol is paralleled by the epimerisation of 2 : 4-3 : 5-dimethylene D-manno- and D-gluco-saccharic acid. When a solution of the dimethyl ester of either of these acids is boiled with barium hydroxide solution, epimerisation occurs with the formation of 2 : 4-3 : 5-dimethylene L-ido-saccharic acid (IX) (Haworth, Jones, Stacey, and Wiggins, *J.*, 1944, 61). In this case,

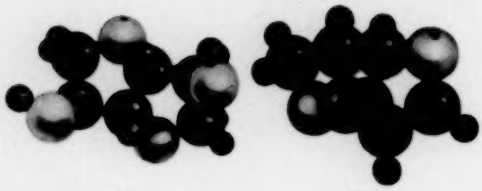


however, the ready isolation of dimethylene L-idosaccharic acid may be caused merely by the ease with which this substance crystallises or to its lower solubility. In fact the alkaline hydrolysis of dimethyl dimethylene D-glucosaccharate did afford some dimethylene D-glucosaccharic acid as well as the L-idosaccharic acid derivative. On the other hand, similar treatment of the corresponding mannosaccharic acid derivative gave only (IX).

Another example of the conversion of 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol into dianhydro-L-iditol is given by Fletcher and Goepp (*J. Amer. Chem. Soc.*, 1946, **68**, 939), who treated each of these derivatives with Raney nickel and then hydrogenated them in the presence of that catalyst. Again dianhydro-L-iditol was the only product isolated in quantity. Lew, Wolfrom, and Goepp (*J. Amer. Chem. Soc.*, 1945, **67**, 1865) however claim to have demonstrated the presence of all three dianhydrides in the reaction product, by chromatographic methods.



(1) (2)



(3) (4)

(1) 1 : 4-3 : 6-*Dianhydro*-D-*mannitol*.
(2) 1 : 4-3 : 6-*Dianhydro*-D-*sorbitol*.
(3) 1 : 4-3 : 6-*Dianhydro*-D-*iditol*.
(4) 2 : 5-*Imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol* (*inverted to show the imine bridge*).

[*To face p.* 373.

In order to test whether the deamination of **2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-L-iditol** would lead solely to the formation of dianhydro-L-iditol the attempt was made to prepare this diamine. **1 : 4-3 : 6-Dianhydro-L-iditol** was converted into the **2 : 5-*di*-toluene-p-*sulphonate*** and this treated with methyl-alcoholic ammonia in the manner found successful for the preparation of the diamines of dianhydro-mannitol and -sorbitol (Montgomery and Wiggins, *J.*, 1946, 393). No diamine was obtained however; instead a substance having only one nitrogen atom per six carbon atoms was isolated. This was a base, $C_6H_9O_3N$, which had m. p. 99—100°, $[\alpha]_D$ +90·5°, and formed a crystalline *oxalate*, *picrate*, and *hydrochloride*. It gave no Schiff base with salicylaldehyde; it lost no nitrogen on treatment with nitrous acid, but afforded a crystalline *N*-nitroso-derivative giving the characteristic Liebermann colour reaction with phenol and sulphuric acid. The compound $C_6H_9O_3N$ is therefore a dianhydrohexitol containing a secondary amino-group, and the only way in which this can be reconciled with the analytical data of the compound and its derivatives is to assume the formation of an imine bridge between $C_{(2)}$ and $C_{(5)}$. An immediate difficulty arises as scale models show that it is impossible so to join $C_{(2)}$ to $C_{(5)}$ of the **1 : 4-3 : 6-dianhydro-L-iditol**. The imino-compound $C_6H_9O_3N$ must therefore possess a different configuration. Since the reaction conditions preclude the likelihood of there being any alteration to the ring structure and hence of the configuration about $C_{(3)}$ and $C_{(4)}$ the only possible configurations are those of D-mannitol and D-sorbitol. Configurational changes about $C_{(2)}$ and $C_{(5)}$ are certainly possible because the removal of toluene-*p*-sulphonyloxy-groups by alkaline reagents must involve the transitory formation of the carbonium cation (VIII). From scale models of the three epimerically related **1 : 4-3 : 6-dianhydrohexitols** (shown in the figure) it is clear that the only one in which $C_{(2)}$ and $C_{(5)}$ could be bridged by an imine group is **1 : 4-3 : 6-dianhydro-D-mannitol**. Hence it is tentatively suggested that the compound $C_6H_9O_3N$ obtained by the action of ammonia on **2 : 5-di-toluene-*p*-sulphonyl 1 : 4-3 : 6-dianhydro-L-iditol** is **2 : 5-*imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol*** (X).

Experimental.

Deamination of **2 : 5-*Diamino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxysorbitol***.—The diamine (3·95 g., prepared according to Montgomery and Wiggins *J.*, 1946, 393) was dissolved in water (25 c.c.) and acidified with dilute hydrochloric acid. Sodium nitrite (4·5 g.) dissolved in water (25 c.c.) was then added and the mixture kept overnight. Thereafter the solution was neutralised with barium carbonate, filtered, and evaporated to dryness under reduced pressure. The dry residue was extracted exhaustively with hot ethyl acetate, and the extracts were evaporated to a syrup (1·68 g.). This distilled at 115—130° (bath temperature)/0·05 mm. as a light-yellow oil (1·27 g.), $[\alpha]_D$ +46·7° (*c*, 1·9 in acetone). A portion (0·9 g.) of this distillate was dissolved in dry pyridine (15 c.c.), and methanesulphonyl chloride (1·6 c.c.) added at 0°. After being kept overnight at room temperature, the mixture was poured into water and extracted therefrom with chloroform. The chloroform extract was washed successively with dilute sulphuric acid, sodium hydrogen carbonate solution, and with water, dried ($MgSO_4$), filtered (charcoal), and evaporated to dryness. The residue, crystallised and recrystallised from alcohol, gave needles of **2 : 5-dimethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol**, m. p. 156·5° alone or on admixture with authentic material, and had $[\alpha]_D$ +48·0° (*c*, 2·1 in acetone). Further crops of crystals were obtained from the mother-liquors but no other pure substance could be isolated.

Deamination of **2 : 5-*Diamino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxymannitol***.—The diamine (1·29 g.) (Montgomery and Wiggins, *loc. cit.*) was dissolved in water (30 c.c.), acidified with glacial acetic acid (3 c.c.), and treated with sodium nitrite (1·3 g.). The solution was kept overnight at room temperature and worked up as above. The resultant syrup distilled at 175—180° (bath temperature)/0·001 mm. By repetitions 3·52 g. of the distillate were accumulated. This was treated in dry pyridine (40 c.c.) with methanesulphonyl chloride (9·33 c.c.) at 0°. Thereafter the mixture was kept at room temperature overnight and then poured into water (300 c.c.). A solid (0·76 g.) was deposited and after being recrystallised from methyl alcohol had m. p. 156—157° alone or on admixture with **2 : 5-dimethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol**, and $[\alpha]_D$ +48·0° (*c*, 2·1 in acetone). For the isomers of this product see Montgomery and Wiggins (*J.*, 1948, 2204) and Bashford and Wiggins (*J.*, 1948, 299).

2 : 5-*Ditoluene*-p-*sulphonyl* 1 : 4-3 : 6-*Dianhydro*-L-*iditol*.—To **1 : 4-3 : 6-dianhydro-L-iditol** (17·3 g.; Wiggins, *J.*, 1948, 1403) in dry pyridine (75 c.c.) toluene-*p*-sulphonyl chloride (50 g.) was added a little at a time at 0°. The mixture was kept at room temperature for 72 hours and thereafter poured into water. The solid which separated was filtered off, washed, and dried; recrystallised from ethyl alcohol, **2 : 5-*ditoluene*-p-*sulphonyl* 1 : 4-3 : 6-*dianhydro*-L-*iditol*** (44 g.) formed needles, m. p. 90°, $[\alpha]_D$ +38·2° (*c*, 2·0, in chloroform) (Found: C, 52·8; H, 5·1. $C_{20}H_{22}O_7S_2$ requires C, 52·8; H, 4·85%).

Reaction of **2 : 5-*Di*-toluene-p-*sulphonyl* 1 : 4-3 : 6-*Dianhydro*-L-*iditol with Methyl-alcoholic Ammonia***.—The compound (42 g.) was mixed with dry methyl alcohol (900 c.c.), saturated at 0° with dry ammonia gas, and heated in an autoclave for 30 hours at 160—170°. Thereafter the solution was evaporated to dryness, and the residue heated at 100° with barium hydroxide (50 g.) in water (400 c.c.) (this and all subsequent operations were carried out in an atmosphere of nitrogen). The solution was then evaporated to a syrup under reduced pressure, the water being completely removed by distillation with benzene. The residue was extracted several times with boiling chloroform, and the combined extracts were filtered and evaporated to dryness. The residue, recrystallised from ethyl acetate, formed needles, m. p. 99—100°, $[\alpha]_D$ +90·5° (*c*, 2·56 in chloroform) (2·0 g.). This substance was very volatile and

readily sublimed, and it is probable that a large amount of the material was lost during the isolation. It did not form a Schiff base with salicylaldehyde and a trace of alkali. It was 2 : 5-*imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol* [Found : C, 56·4; H, 6·9; N, 10·7%; *M* (Rast), 136·5. $C_8H_{13}O_4N$ requires C, 56·6; H, 7·1; N, 11·0%; *M*, 127]. The imine (0·05 g.) was dissolved in alcohol (2 c.c.), and picric acid (0·1 g.), also dissolved in alcohol (2 c.c.), was added. Recrystallised from alcohol the *picrate* which separated formed yellow needles (0·11 g.), m. p. 219—220° (decomp.) (Found : N, 16·3. $C_{19}H_{16}O_{11}N_6$ requires N, 15·8%). The imine (0·07 g.) was dissolved in chloroform (4 c.c.), and the solution saturated with dry hydrogen chloride. After a few seconds a white precipitate separated. The *hydrochloride*, recrystallised from alcohol containing a trace of water, had m. p. 280—290° (decomp.) (Found : C, 44·1; H, 6·0; N, 6·3. $C_8H_{14}O_4N,HCl$ requires C, 44·3; H, 6·1; N, 6·6%). The imine (0·05 g.) in alcohol (2 c.c.) was treated with an equivalent amount of oxalic acid also dissolved in alcohol. A white solid separated. The mixture was heated to the b. p., and water added drop by drop until complete dissolution was effected. On cooling, the *oxalate* separated; it had m. p. 243° (Found : C, 48·6; H, 5·5. $C_{12}H_{18}O_8N_2$ requires C, 48·8; H, 5·81%).

The mother-liquors after the separation of the imino-compound were concentrated and distilled in two portions : (*a*) b. p. 100° (bath temperature)/0·1 mm. (0·3 g.), and (*b*) b. p. 120—140° (bath temperature)/0·1 mm. (1·52 g.). Fraction (*a*) yielded a further amount of 2 : 5-imino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-D-mannitol, but fraction (*b*) was a liquid which has not been identified.

N-Nitroso-derivative of 2 : 5-*Imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol*.—The imine (0·5 g.) was dissolved in water, acidified with acetic acid, and treated with sodium nitrite (0·5 g.) dissolved in water, and the mixture kept at room temperature overnight. No evolution of nitrogen was apparent. The solution was neutralised with sodium hydrogen carbonate and evaporated to dryness, and the dry residue exhaustively extracted with hot ethyl acetate. The combined extracts on being evaporated afforded a solid which, recrystallised from ethyl acetate, furnished the *N-nitroso*-derivative, m. p. 121·5°, $[\alpha]_D$ −323° (*c*, 2·43 in chloroform), which gave the characteristic Liebermann test for *N*-nitroso-compounds (Found : C, 45·6; H, 5·1. $C_8H_{12}O_5N_2$ requires C, 46·2; H, 5·1%).

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83. *Photochemical Reactions. Part XV.* (a) *Photopolymerisation of Coumarins and Related Substances.* (b) *Photo-addition and -reduction Processes of Aromatic Ketones.*

By ALEXANDER SCHÖNBERG, NAZIH LATIF, RADWAN MOUBASHER, and (in part) WILLIAM IBRAHIM AWAD.

(*a*) 3-Phenylcoumarin forms a photodimer analogous to that from coumarin; the constitution of the latter dimer is therefore (Ia) and not (II). Photodimers of 3-phenylisocoumarin and benzylidenephthalide were obtained (cf. IV and III). These dimers gave the monomers when heated.

(*b*) From 2 : 7-dimethylphenanthraquinone with stilbene and from phenanthraquinone with 1 : 2-di-4′-pyridylethylene, 3 : 4-diphenyl- and 3-phenyl-isocoumarin and 1 : 3-diphenylisochromen, the photo-products (V), (VI), (VIII), (VII), and (IX) respectively were obtained.

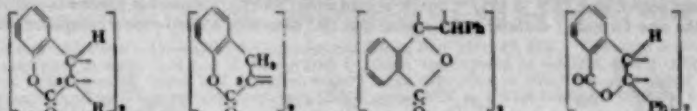
o-Dibenzoylbenzene in *iso*propyl alcohol yielded a photoproduct which, when heated, gave 1 : 3-diphenylisobenzofuran (XI). Phenanthraquinone monoxime and monoimine on photoreduction yielded diphenanthro-oxazine (XIII); with aromatic aldehydes in the presence of light the oxime yielded products which gave 2-arylphenanthro-oxazoles (X) on heating.

In connection with the constitution of the photoreduction product of triketoindane (XIV) the constitution of a substance erroneously described (Gabriel and Leupold, *Ber.*, **1898**, **31**, 1159) as (XVII) is proved to be (XXI).

Photopolymerisations.—(a) *Coumarins.* Formulæ (Ia) and (II) have been discussed for the product obtained when a solution of coumarin in alcohol or a suspension of the solid in water is exposed to sunlight (Ciamician and Silber, *Ber.*, 1902, **35**, 4130; 1903, **36**, 4266; De Jong, *Rec. Trav. chim.*, 1924, **43**, 318). Formula (II) is still widely used (cf. Richter and Anschütz, "Chemie der Kohlenstoffverbindungen," Vol. II, 2nd half, p. 515, 12th edn., 1935). Fischer has given to the photodimer of umbelliferone methyl ether a formula analogous to (II) (*Arch. Pharm.*, 1941, **279**, 306), but its correctness was questioned by Wessely and Flaichinger (*Ber.*, 1942, **75**, 971).

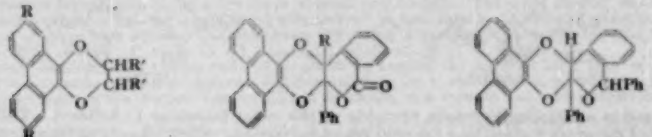
Photodimerisation of coumarin and its derivatives with the formation of (II) or its analogues is possible only when the hydrogen in the position 3 is unsubstituted. We found, however, that 3-phenylcoumarin in sunlight is easily converted in excellent yield into a similar *photodimer*; therefore, the dimers must be *cyclo*butane derivatives (I), a conception which is favoured by

regeneration of the monomer when the photodimer of coumarin or of 3-phenylcoumarin is heated.



(I; *a*, R = H; *b*, R = Ph.) (II.) (III.) (IV.)

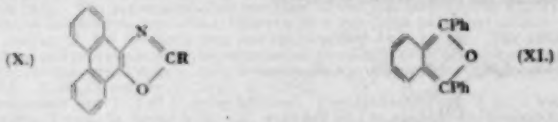
(b) ***Benzylidenephthalide and 3-phenylisocoumarin.*** Both these substances form *photodimers* (III and IV, respectively) under the action of sunlight; when heated, the products regenerate the monomers.



(V; R = Me, R' = Ph.) (VI; R = H, R' = C_5H_4N.) (VII; R = H.) (VIII; R = Ph.) (IX.)

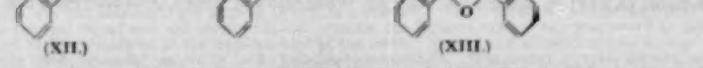
Photoaddition Reactions.—We have continued the investigations on the action of phenanthraquinone on ethylenes (Schönberg, Mustafa, and their co-workers, *J.*, 1944, 387; 1945, 551; 1948, 2126) and have studied the action of 2 : 7-dimethylphenanthraquinone on stilbene and of phenanthraquinone on 1 : 2-di-4'-pyridylethylene, 3 : 4-diphenyl- and 3-phenyl-*iso*coumarin, and 1 : 3-diphenyl*iso*chromen. In all cases colourless or almost colourless addition *products* (V)—(IX) were obtained, some of which, *e.g.*, (VII) and (VIII), regenerated the starting materials when heated.

Phenanthraquinone Monoxime and Aromatic Aldehydes.—The oxime and benzaldehyde do not react in benzene in the dark; in sunlight, however, a product was formed which on heating yielded 2-phenylphenanthro-oxazole (X; R = Ph); in the case of anisaldehyde 2-p-*methoxyphenylphenanthro-oxazole* (X; R = C_6H_4·OMe-*p*) was obtained. These reactions are similar to the photo-formation of 2-arylphenanthro-oxazoles by the action of aromatic aldehydes on phenanthraquinoneimine (Schönberg and Awad, *J.*, 1945, 197).



(X.) (XI.)

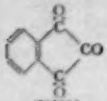
Photoreductions.—Very little is known about the photoreduction of *o*-diketones, *o*-quinone oximes or imines. When *o*-dibenzoylbenzene was exposed to sunlight in *iso*propyl alcohol, a yellow crystalline product was obtained which, when heated, gave 1 : 3-diphenyl*iso*benzofuran (XI) in good yield. Phenanthraquinone monoxime or imine (XII) in *iso*propyl alcohol in sunlight gave diphenanthro-oxazine (XIII) in good yield, probably by way of 10-aminophenanthr-9-ol.



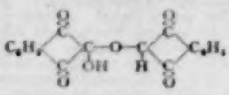
(XII.) (XIII.)

Previously it was shown (Schönberg and Moubasher, *J.*, 1944, 366) that when triketoindane (XIV) in *iso*propyl alcohol was exposed to sunlight and the reaction product crystallised from a mixture containing water, a compound known as hydrindantin was formed, which previously had been obtained by Ruhemann (*J.*, 1911, **99**, 797) by reduction of ninhydrin (the hydrate of

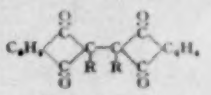
XIV) in the absence of light. Ruhemann believed that hydrindantin was (XV + $2H_2O$), but recently Schönberg and Moubasher (*J.*, 1949, 212) showed that the reactions of this compound do not accord with (XV + $2H_2O$), but do accord with (XVIII). However, there was one obstacle to the new formula : Gabriel and Leupold (*loc. cit.*) described a deep-yellow compound obtained



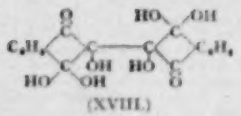
(XIV.)



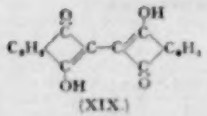
(XV.)



(XVI; R = H.)
(XVII; R = OH.)



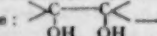
(XVIII.)



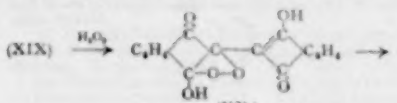
(XIX.)

by the action of alkaline hydrogen peroxide on the violet bisindane-1 : 3-dionyl. This yellow compound for which Gabriel and Leupold advanced formula (XVII) cannot be transformed into hydrindantin by the action of water. For the violet compound Gabriel and Leupold erroneously advanced formula (XVI); it has in reality formula (XIX) (cf. Schönberg and Moubasher, *J.*, 1944, 366).

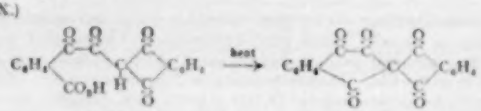
Gabriel and Leupold's oxidation scheme (XVI) ⟶ (XVII) has to be replaced by (XIX) ⟶ (XX) ⟶ (XXI). Formula (XXI) but not (XVII) is in agreement with the deep-yellow colour of the compound and its solubility in sodium hydrogen carbonate solution with evolution of carbon dioxide and its vigorous reaction with diazomethane. *o*-(1 : 3-Diketoindanyl-2-glyoxyloyl)benzoic acid (XXI) on pyrolysis yields indane-1 : 3-dione-2-*spiro*-2′-(1′ : 3′ : 4′-triketo-1′ : 2′ : 3′ : 4′-tetrahydronaphthalene) (XXII) (cf. Radulescu, *Zentr.*, 1923, III, 1081).

If formula (XVI) were correct, then, on heating, (XVII) should decompose according to the scheme :  (cf. Schönberg and Mustafa, *J.*, 1944, 305).

Formula (XXI) explains readily the nature of the product actually obtained by pyrolysis, namely (XXII). The hypothetical change (XVII) ⟶ (XXII) can take place only in consequence of a pinacolin rearrangement ; however, such rearrangement is not effected by pyrolysis alone, but by heating the pinacols with acids, etc.

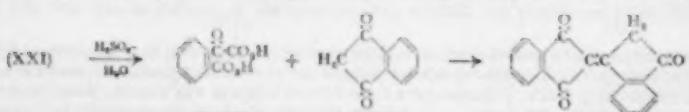


(XX.)



(XXI.) (XXII.)

Acid hydrolysis of (XXI) yields phthalonic acid (XXIII) and 2-(3-ketoindan-1-ylidene)-indane-1 : 3-dione (XXV), which is believed to be formed from the primary product (indane-1 : 3-dione) (XXIV) by autocondensation (cf. Wislicenus and Kötzle, *Annalen*, 1889, 252, 79).



(XXIII.) (XXIV.) (XXV.)

Experimental.

The photochemical reactions were carried out in Pyrex glass tubes, the air having been displaced by dry carbon dioxide and the tube sealed. "AnalaR" benzene which had been dried over sodium was used.

Photopolymerisations.—Coumarin (cf. Ciamician and Silber, *Ber.*, 1914, **47**, 642). Powdered coumarin (3 g.), suspended in water (100 c.c.) in a stoppered 1-l. flask, was exposed to sunlight during October. The solid was filtered off, dried, and extracted several times with ether in which the photodimer was slightly soluble. The dimer recrystallised from glacial acetic acid in almost colourless crystals, m. p. *ca.* 260° (decomp.) (*ca.* 10% yield).

The photodimer was heated under water-pump vacuum at 290° (bath) in a Pyrex test-tube for 1 hour. Oily drops of coumarin (m. p. and mixed m. p.) which accumulated on the upper parts of the reaction vessel solidified after being allowed to cool in a vacuum.

3-Phenylcoumarin. 3-Phenylcoumarin (1 g.) (Meerwein *et al.*, *J. pr. Chem.*, 1939, **152**, 253) in benzene (25 c.c.) was exposed to sunlight during October. Crystals separated gradually, were filtered off, and were washed with ether. A further quantity of the crude photodimer was obtained on concentration of the benzene filtrate, addition of a few drops of ether, and cooling. The crude product was dissolved in the least amount of hot benzene, filtered hot, and left to cool slowly; to the still warm solution, a few drops of ether were added. The *photodimer* (Ib) slowly separated in colourless crystals, m. p. *ca.* 242° (*ca.* 90%) (Found: C, 81·1; H, 4·7. $C_{36}H_{28}O_4$ requires C, 81·1; H, 4·5%).

Thermal decomposition was carried out as above by heating the material for 1 hour in a boiling ethyl phthalate bath. The oily droplets of 3-phenylcoumarin (m. p. and mixed m. p.) which accumulated at the upper parts of the reaction vessel solidified on cooling in a vacuum and were recrystallised from ethyl alcohol.

3-Phenylisocoumarin. 3-Phenylisocoumarin (1 g.) (Gabriel, *Ber.*, 1885, **18**, 2445) in benzene (30 c.c.) was exposed to sunlight for 25 days (November) and the crystals which separated were filtered off and washed several times with ether. A further quantity of the crude product was obtained on concentrating the benzene filtrate and allowing it to cool slowly to room temperature. The *photodimer* (IV) recrystallised from benzene in colourless crystals, m. p. 254° (yield almost quantitative) (Found: C, 80·7; H, 4·7. $C_{36}H_{28}O_4$ requires C, 81·1; H, 4·5%).

The photodimer was heated as described previously at 300° for 30 minutes and then left to cool in a vacuum, and the crystals of 3-phenylisocoumarin (m. p. and mixed m. p.), which formed on the upper parts of the vessel, recrystallised from dilute alcohol.

Benzylidenephthalide. Benzylidenephthalide (*ca.* 1·5 g.) (Gabriel, *Org. Synth.*, Vol. XIII, 10) in benzene (25 c.c.) were exposed to sunlight for 10 days (January). The small amount of colourless crystals which separated was filtered off. The benzene filtrate was concentrated, left to cool slowly, and, while still warm treated with a few drops of ether. On cooling in ice, a colourless crystalline solid separated out, having m. p. *ca.* 206°. For purification, the *dimer* was treated again similarly with benzene–ether and then had m. p. 202—215° [Found: C, 81·6; H, 4·3%; *M* (Rast), 507. $C_{36}H_{28}O_4$ requires C, 81·1; H, 4·5%; *M*, 445].

The photodimer was heated at 260° for 40 minutes under reduced pressure. Oily drops of benzylidenephthalide (m. p. and mixed m. p.) which accumulated on the upper parts of the reaction vessel solidified on cooling slowly under reduced pressure. They were recrystallised from benzene.

Photoreactions.—2 : 7-Dimethylphenanthraquinone and stilbene. 2 : 7-Dimethylphenanthraquinone (0·5 g.) (Lieberman, *Ber.*, 1911, **44**, 1453) and stilbene (0·4 g.) in benzene (20 c.c.) were exposed to sunlight for one week in May. The benzene solution was then filtered and concentrated almost to dryness, and a small amount of hot acetone was added, followed by a few drops of methyl alcohol. A yellow solid separated on cooling (in the ice-chest) and was recrystallised from xylene. The addition *product* (V) formed almost colourless crystals which decomposed at about 258° to an orange-brown melt. It gave no colour with cold concentrated sulphuric acid, but on gentle warming a violet colour was observed (Found: C, 86·0; H, 5·3. $C_{30}H_{22}O_2$ requires C, 86·5; H, 5·7%).

Phenanthraquinone and 1 : 2-di-4′-pyridylethylene. Phenanthraquinone (1 g., 1 mol.), and 1 : 2-di-4′-pyridylethylene (1 mol.) in benzene (30 c.c.) were exposed to sunlight in November. After 7 days, the crystals which separated were filtered off and washed with hot acetone, in which the initial components were soluble. The colouless residue of the *adduct* (VI) obtained was washed with 5% sodium hydroxide solution, then with alcohol, and lastly with ether, and decomposed at *ca.* 187° to an orange melt (Found: C, 79·4; H, 4·6; N, 7·7. $C_{38}H_{24}O_2N_2$ requires C, 80·0; H, 4·6; N, 7·2%).

Phenanthraquinone and 3 : 4-diphenylisocoumarin. Phenanthraquinone (0·7 g.) and 3 : 4-diphenylisocoumarin (1 g.) (Koelsch and Le Claire, *J. Amer. Chem. Soc.*, 1943, **65**, 754) were exposed to sunlight in benzene (50 c.c.) for 20 days (December). The benzene solution was filtered, concentrated, and left to cool slowly, almost colourless crystals of the addition *product* (VIII) separating. These recrystallised from benzene in colourless crystals which decomposed at *ca.* 267° to a reddish brown melt. They gave no colour reaction with concentrated sulphuric acid, and were insoluble in cold or warm sodium hydroxide solution (*ca.* 5%) (Found: C, 83·1; H, 4·7. $C_{38}H_{26}O_4$ requires C, 83·0; H, 4·8%).

(VIII) was heated under reduced pressure (water-pump vacuum) at 300° (bath temperature) for 15 minutes in a test tube and then allowed to cool in a vacuum. The crystals formed on the upper parts of the reaction vessel were extracted with cold benzene, the benzene extract was evaporated to dryness, and the residue dissolved in the least amount of hot methyl alcohol and allowed to cool slowly. The crystals which separated proved to be 3 : 4-diphenylisocoumarin. The orange crystals left undissolved after benzene extraction were recrystallised from boiling benzene and proved to be phenanthraquinone (m. p. and mixed m. p.).

Phenanthraquinone and 3-phenylisocoumarin. Phenanthraquinone (1 g.) and 3-phenylisocoumarin (1·1 g.) in benzene (30 c.c.) were exposed to sunlight for 2 days (May). A heavy crystalline deposit of *adduct* (VII) began to separate after a few hours. This was filtered off and recrystallised from xylene

in almost colourless crystals decomposing to a reddish-brown melt at about 270° and giving no colour reaction in sulphuric acid (Found: C, 80·8; H, 4·3. $C_{29}H_{18}O_4$ requires C, 80·9; H, 4·2%).

(VII) was heated as was (VIII). The crystals formed on the upper parts of the reaction vessel were extracted several times with cold methyl alcohol; uniform orange crystals melting at 196° were left and gave, with concentrated sulphuric acid, the olive-green colour reaction of phenanthraquinone. On concentration of the methyl-alcoholic extract, crystals which separated out proved to be 3-phenylisocoumarin (m. p. and mixed m.p.).

Phenanthraquinone and 1 : 3-diphenylisochromen. Phenanthraquinone (0·25 g.) and 1 : 3-diphenylisochromen (0·3 g.) (Schmidlin and Bannus, *Ber.*, 1912, **45**, 3202) partly suspended in benzene (30 c.c.) were exposed to sunlight for one week (May). The benzene solution was filtered, concentrated to small volume, and treated with light petroleum (b. p. 60—80°), which caused precipitation. The supernatant fluid was decanted, and the residual *adduct* (IX) washed with cold alcohol and recrystallised from benzene–acetone. It recrystallised from xylene in colourless crystals, decomp. *ca.* 300° to a reddish-brown melt (Found: C, 85·4; H, 5·3. $C_{33}H_{24}O_2$ requires, C, 85·3; H, 4·9%).

Photoreductions.—o-Dibenzoylbenzene. *o*-Dibenzoylbenzene (1·3 g.) (Simonis and Remmert, *Ber.*, 1915, **48**, 206) in isopropyl alcohol (30 c.c.) was exposed to sunlight for 30 days (April). The yellow crystals formed were filtered off from the fluorescent benzene solution and recrystallised from chloroform in yellow needles m. p. *ca.* 160°. They gave no colour reaction with concentrated sulphuric acid (*o*-dibenzoylbenzene gives a red colour), but in chloroform solution a green fluorescence was noted. The photo-product was heated under reduced pressure (oil-pump vacuum) in a Pyrex test-tube at 200° (bath temperature) for 1 hour and then allowed to cool slowly in a vacuum. After 24 hours a crystalline mass appeared near the bottom of the reaction vessel (most of the material used) and some yellow crystals on the upper part, which was not in contact with the bath. The lower crystalline mass recrystallised from alcohol in yellow crystals which proved to be 1 : 3-diphenylisobenzofuran (XI) (m. p. and mixed m. p.) (80% yield). Both the decomposition product and an authentic specimen gave a red colour with concentrated sulphuric acid, fugitive at room temperature. The decomposition product gave the brilliant green fluorescence described by Guyot and Catel (*Compt. rend.*, 1905, **140**, 1349).

Phenanthraquinone monoxime.* The oxime (0·5 g.) in isopropyl alcohol (25 c.c.) was exposed to sunlight for a fortnight (June). The brown deposit was filtered off and crystallised from 2-methylnaphthalene in very small brown crystals showing a green lustre; on pulverisation a brown powder was produced. It gave the characteristic blue colour of diphenanthro-oxazine with concentrated sulphuric acid and had m. p. above 305° (Found: N, 4·0. Calc. for $C_{28}H_{17}ON$: N, 3·7%) (yield, almost quantitative).

Phenanthraquinone imine. The experiment was carried out as previously described and the product (almost quantitative yield) crystallised from 2-methylnaphthalene in very small brown crystals showing a green lustre, giving a brown powder on pulverisation and the characteristic blue colour with concentrated sulphuric acid, and having m. p. above 305° (Found: N, 4·2. Calc. for $C_{28}H_{17}ON$: N, 3·7%).

Photochemical Reaction between Aldehydes and Phenthraquinone Monoxime.—With benzaldehyde. Phenanthraquinone monoxime (0·5 g.) and benzaldehyde (1 g.) in benzene (25 c.c.) were exposed to sunlight for 15 days (May) (in a Monax glass vessel); a colourless deposit was formed which was filtered off. The solution was concentrated under reduced pressure and the product recrystallised from benzene in almost colourless crystals, m. p. 256° (decomp.) depending on the rate of heating.

In a parallel experiment in the absence of light phenanthraquinone monoxime was recovered unchanged almost quantitatively.

When the photo-product was heated in a boiling ethyl cinnamate bath (b. p. 271°) in a carbon dioxide atmosphere for ½ hour, a colourless crystalline sublimate was obtained which proved to be 2-phenylphenanthro-oxazole, m. p. 204° undepressed on admixture with an authentic specimen prepared according to Stein and Day (*J. Amer. Chem. Soc.*, 1942, **64**, 2567).

With anisaldehyde. The oxime (0·5 g.) and aldehyde (1 g.) in benzene (25 c.c.) were exposed to sunlight (Monax glass vessel) for one week (April). The colourless deposit, recrystallised from absolute ethyl alcohol, had m. p. 244°, gave a yellowish-brown colour with concentrated sulphuric acid, and, when heated in an ethyl cinnamate bath, as described in the case of benzaldehyde, gave an almost colourless crystalline sublimate of 2-*p*-*methoxyphenylphenanthro-oxazole* (X; R = C_6H_4·OMe-*p*), m. p. 178° (Found: C, 80·9; H, 4·7; N, 4·4. $C_{29}H_{19}O_2N$ requires C, 81·2; H, 4·6; N, 4·3%).

This oxazole was also prepared as follows: Equimolecular amounts of phenanthraquinone imine and anisaldehyde (freshly distilled), dissolved in absolute alcohol containing few drops of piperidine, were refluxed for 1 hour. On cooling (and if necessary concentration of the solution) a deposit was formed which, crystallised from alcohol, had m. p. 178°, not depressed on admixture with the substance obtained as above.

o-(1 : 3-*Dihetoindanyl-2-glyoxyloyl*)*benzoic Acid* (XXI).†—(XXI) was prepared from bisindane-1 : 3-dionyl (XIX) according to the directions given by Gabriel and Leupold (*loc. cit.*) for the preparation of the supposed (XVII).

Pyrolysis was carried out in a boiling-tube, connected with a vacuum pump, the lower part being immersed in a bath at 250°; the heating was for 30 minutes. Crystals of (XXII) were formed on the cold parts of the reaction vessel; they recrystallised from acetic acid in orange needles, m. p. 222—225°, undepressed on admixture with an authentic sample (cf. *loc. cit.* and Radulescu, *loc. cit.*) (Found: C, 70·8; H, 2·7. Calc. for $C_{18}H_8O_3$: C, 71·0; H, 2·6%) (yield about 40%).

A suspension of (XXI) (0·3 g.) in dilute sulphuric acid (20 c.c. of concentrated acid in 100 c.c. of water) was heated on a water-bath for 3 hours. The reaction mixture was concentrated to about 50 c.c., whereupon a yellow substance (A) separated from the solution (B). (A) recrystallised from ethyl alcohol as pale yellow needles, m. p. 208° (brown melt), and was proved to be the 2-(3-ketoindan-1-ylidene)-

* The experiments with phenanthraquinone monoxime and imine were carried out by William Ibrahim Awad.

† These experiments were carried out by Radwan Moubasher.

indane-1 : 3-dione (XXV) by m. p. and mixed m. p. determinations with an authentic specimen prepared according to Wislicenus and Kötzle (*loc. cit.*). It dissolved in concentrated sulphuric acid, giving an orange colour. (B) was heated for 30 minutes on the water-bath, allowed to cool and filtered; and the filtrate was extracted several times with ether, from which colourless crystals were then obtained; recrystallised from ether in colourless needles, m. p. 145° (decomp.), they proved to be phthalonic acid (XXIII) (m. p. and mixed m. p.).

Di-(2-hydroxy-1 : 3-dioxindan-2-yl) (XVII).—Hydrindantin (XVIII) (1 g.) was refluxed with oxalyl chloride (10 g.) for 10 minutes, with a calcium chloride safety tube. The reaction product was evaporated to dryness in a vacuum, moisture being excluded, and the residue crystallised from benzene (anhydrous); colourless crystals were obtained, having m. p. *ca.* 235° (decomp.). The *product* (XVII) gave an orange-yellow colour with concentrated sulphuric acid (Found: C, 66·9; H, 3·3. $C_{18}H_{10}O_6$ requires C, 67·1; H, 3·1%).

The product, suspended in ether, was shaken at room temperature with water for about 30 minutes; the solid was then collected and proved to be (XVIII). (XVII) and (XVIII) are decomposed by alkali with the formation of a blue solution, containing probably the salt of the enolic form of 2-hydroxyindane-1 : 3-dione and the hydrate of (XIV) (ninhydrin).

The authors thank Dr. H. I. Thayer, Pittsburgh, Pa., for the gift of 1 : 2-di-4'-pyridylethylene.

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84. *Studies in Light Absorption. Part IX. The Relation between Absorption Intensities and Molecular Dimensions, and its Application to the Electronic Spectra of Polyenes and Polycyclic Benzenoid Hydrocarbons.*

By E. A. Braude.

The maximum possible extinction coefficients of molecules can be calculated in a simple manner from the molecular dimensions (cf. Braude, *Nature*, 1945, **155**, 753). The actual extinction coefficients for allowed transitions can be calculated from considerations of the effective "chromophore area" and the polarisation direction of the light absorbed. The values thus obtained for polyenes and polycyclic benzenoid hydrocarbons are in good agreement with those observed.

The intensities of molecular spectra have received increasing attention within recent years from the experimental as well as from the theoretical point of view. On the one hand, the accurate determination of absorption intensities has become an essential feature of the development of absorption spectroscopy as an analytical tool; and, on the other, the calculation of extinction coefficients by the methods of wave mechanics has been attempted by several authors (Mulliken, *J. Chem. Physics*, **1939**, **7**, 14, 20, 339, 353, 356, 364, 570; Sklar, *ibid.*, 984; *Rev. Mod. Physics*, **1942**, **14**, 232; Bayliss, *J. Chem. Physics*, **1948**, **16**, 287; Kuhn, *Helv. Chim. Acta*, **1948**, **31**, 1780; Coulson, *Proc. Physical Soc.*, **1948**, **60**, 257). These calculations, whilst of great value in helping to establish the nature of the transitions involved, have not been entirely successful quantitatively since they involve the experimental frequency of the absorption band and lead to absorption-intensity values which generally differ in order of magnitude from those observed unless empirical correction factors are introduced.

The present paper sets out a theory of absorption intensities based solely on considerations of molecular geometry, an approach which appears to have been entirely neglected in the past. It is possible to calculate, in a very simple manner, the maximum possible extinction coefficient of a molecule, the only assumption being that the light must fall within the space of the molecular dimensions in order to be absorbed. Such a calculation is quite independent of the nature of the transition or the frequency of the light. Consider light of intensity I falling on a slice of thickness δl of a cell of unit area filled with the vapour or a dilute solution in a transparent solvent of the absorbent at a concentration of c g.-mol./l. Let the average cross-sectional area of the molecule in the plane perpendicular to the direction of the incident light be $[a]$ and let the thickness of the slice be sufficiently small so that there is no superposition of molecules in the direction of propagation of the light. Then we have

Illumination falling on molecules =
(area of molecules/total area) × total illumination = $cN[a]\delta l \,.\, I \times 10^{-3}$

where N is the Avogadro number. Assuming that all the illumination falling on the molecules is absorbed

Illumination absorbed $= -\delta I = cN[a]\delta l \,.\, I \times 10^{-3}$

Integrating this between the limits $l = 0$ and $l = l$

$$[\varepsilon] = 1/cl \,.\, \log_{10}(I_0/I) = 0{\cdot}4343N[a] \times 10^{-3} = 2{\cdot}62 \times 10^{20}[a] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $[\varepsilon]$ is the maximum extinction coefficient. For simple molecules, $[a]$ will be of the order of 10 A.^{2}, *i.e.*, 10^{-15} cm.^{2}, so that $[\varepsilon] \sim 10^5$. This result corresponds in order of magnitude to the highest extinction coefficients which have been observed (cf. below).

According to classical theory, the absorption intensity is determined by the "oscillator strength" (f), *i.e.*, the number of oscillating units per molecule. For electronic transitions

$$f = 2{\cdot}3 \times 10^9 mc^2/Ne^2 \times \int \varepsilon d\nu = 4{\cdot}32 \times 10^{-9} \int \varepsilon d\nu. \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where m and e are the mass and charge of the electron, c is the velocity of light, and $\int \varepsilon d\nu$ is the integrated band area (Ladenburg, *Verh. d. physikal. Ges.*, 1914, **16**, 769; *Z. Physik*, 1921, **4**, 451; *Physical Rev.*, 1933, **43**, 320; Mulliken, *J. Chem. Physics*, 1939, **7**, 14; Förster, *Z. Elektrochem.*, 1939, **45**, 548). Approximately, $\int \varepsilon d\nu = \varepsilon_{max}.\Delta\nu$ where $\Delta\nu$ is the "half-width," *i.e.*, the width of the bands at points where $\varepsilon = \frac{1}{2}\varepsilon_{max}$. $\Delta\nu$ is usually of the order of 5000 cm.$^{-1}$ and for $f = 1$, equation (2) gives $\varepsilon \sim 10^5$. The present treatment thus leads to the same general result as the classical one.

In considering the application of the chromophore-area theory to particular molecules and transitions, at least four factors must be taken into account which will generally reduce the actual extinction coefficient ε considerably below the maximum possible coefficient $[\varepsilon]$. First, in polyatomic molecules the effective chromophore area a will generally be smaller than the maximum cross-sectional area $[a]$ because a given electronic or vibrational transition will be confined to a particular atom or group of atoms and only light falling within the space of the atoms and bonds concerned will be absorbed. Secondly, vibrational and electronic transitions are polarised along a particular axis and only the electric vector of the light in that axis will be effective. For randomly orientated molecules, the statistical factor by which the effective incident intensity, and therefore ε, is reduced, is $\frac{1}{3}$. Thirdly, the ground state of the molecule is usually distributed over a number of vibrational states, and in some cases, over more than one electronic state, and if the transition only take place from a particular sub-level or -levels, the extinction coefficient for a photon of a given magnitude (wave-length) will be further reduced by a fraction (χ) corresponding to the fractional population of the sub-level or -levels concerned. Fourthly, even when other necessary conditions are fulfilled, the interaction probability (κ) may be less than unity. Hence

$$\varepsilon = \kappa \times \chi \times \tfrac{1}{3} \times 2{\cdot}62 \times 10^{20}a = \kappa \times \chi \times 0{\cdot}87 \times 10^{20}a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

In the sequel, discussion will be confined to electronic transitions and we shall assume $\chi = 1$. We shall also assume that, for an *allowed* electronic transition, $\kappa = 1$. Hence

$$\varepsilon = 0{\cdot}87 \times 10^{20}a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

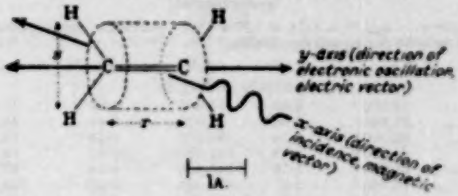
This extremely simple expression for ε involves only one other parameter, the chromophore area a, and should hold for any allowed electronic transition. On this basis the problem of calculating the absorption intensities due to such transitions therefore reduces to the calculation of the chromophore area a.

The application of (3a) can be well illustrated in the polyene and polycyclic hydrocarbon series. The electronic spectra of these have been thoroughly investigated experimentally, and quantitative data for the parent compounds, ethylene and benzene, have recently become available through the work of Klevens, Platt, and their collaborators in the vacuum-ultraviolet region. It is known that the absorption of ethylenic molecules in the visible and ultraviolet regions is due to transitions of the unsaturation (π) electrons. The effective chromophore area a will correspond to the area occupied by the π-electrons (or, more precisely, the area containing a sufficiently high π-electron density) in the plane perpendicular to the line of propagation (magnetic vector) of the light. In order to calculate a it is necessary to know the polarisation direction of the transition since the cross-sectional area will be different in different axes of the elongated polyene and flat polycyclic-hydrocarbon molecules. It is generally accepted on the basis of molecular-orbital theory that the polarisation direction (electric vector) of transitions involving π-electrons is along the axis of the bond, corresponding to a classical direction of incidence (magnetic vector) at right angles to the bond (cf. Bowen, *Ann. Reports*, 1943, **40**, 12).

The polarisation direction can also be deduced from a consideration of chromophore area and the experimentally observed relationship between chain-length and extinction coefficient in the polyene hydrocarbons, taking into account their elongated zig-zag (*trans*)-configuration. Calling the short and long axes of the molecule *x* and *y*, if the electronic oscillation takes place along the *x*-axis, the required classical direction of incidence of the light would be along the *y*-axis, and the effective cross-sectional area would be approximately independent of the length of the polyene chain and the number (n) of ethylenic bonds. Hence, by (3a), ε should be largely independent of n. If, on the other hand, the electronic oscillation takes place along the *y*-axis, *i.e.*, along the axis of the ethylenic bonds, the required classical direction of incidence of the light will be along the *x*-axis, and the effective cross-section of the molecule will increase with the length of the polyene chain. Hence by (3a), ε should also increase with n. This is the relationship experimentally observed (cf. Hausser, Kuhn, and Smakula, *Z. physikal. Chem.*, 1935, **29**, *B*, 385). On the present interpretation, the increase in ε with increasing length of the polyene chain is therefore simply due to the concomitant increase in chromophore area. It will be noted that the deduced polarisation direction is here quite independent of the numerical magnitude of the extinction coefficients but follows directly from the qualitative relationship between ε and n.

FIG. 1.

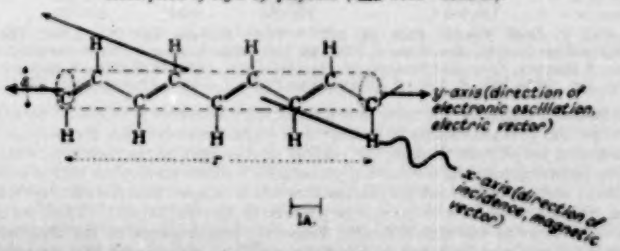
Absorption of light by ethylene ($\lambda_{max.}$ *ca.* 1650 A.).



The required direction of incidence for the transitions under discussion having been established, the chromophore area can readily be estimated. Considering first the parent compound, ethylene, it is clear that the space containing an appreciable π-electron density will be considerably smaller than the total space occupied by the molecule; the carbon–hydrogen bonds have no, or very little, double-bond character and the π-electrons can be regarded as confined to the immediate neighbourhood of the carbon–carbon link. For simplicity, they may be imagined to occupy a cylinder of length r and diameter s (Fig. 1) formed by the lateral

FIG. 2.

Absorption of light by polyenes ($\lambda_{max.}$ 2000—5000 A.).



coalescence of the lobes representing the spatial distribution of the p-electrons of the two carbon atoms (cf. Coulson, *Quarterly Reviews*, 1947, **1**, 144). The effective dimensions of the cylinder will depend on the π-electron density required for interaction with a photon. (More precisely, there will be a region in which the interaction probability is unity, or, at any rate, approximately constant, and beyond which κ rapidly falls.) It is reasonable to assume that the necessary electron-density will be of the same order as the electron-density required for interaction with *X*-rays, and r may therefore be put equal to the carbon–carbon double-bond length 1·35 A.,

whilst s may be estimated from *X*-ray contour diagrams for substituted ethylenes (*e.g.*, stilbene, Robertson and Woodward, *Proc. Roy. Soc.*, 1937, **162**, *A*, 568) to be about 1·5 A. The required chromophore area will be the rectangular cross-section of the cylinder, *i.e.*, $a = 1{\cdot}35 \times 1{\cdot}5 = 2$ A.^{2}, whence, by (3a), $\varepsilon = 17{,}400$. The experimental value, recently determined by Platt, Klevens, and Price (*J. Chem. Physics*, 1949, **17**, 466) is $\varepsilon = 15{,}000$. The agreement is closer than might be expected in view of the approximations involved in the estimation of a.

In butadiene and the higher members of the polyene series, the conventional carbon–carbon single bonds are known to possess appreciable double-bond character and the π-electron density is distributed over the whole chain of carbon atoms. For simplicity, the π-electrons may again be regarded as occupying a cylinder of diameter 1·5 A. and of length corresponding to the distance r between the terminal carbon atoms, taking into account the zig-zag *trans*-configuration of the polyene chain (cf. Bayliss, *J. Chem. Physics*, 1948, **16**, 287) (Fig. 2). The chromophore area is then given by $1{\cdot}5r$ A.^{2}, and, by (3a), $\varepsilon = 1{\cdot}31 \times 10^{20}\,r$. The calculated and observed values are shown in the Table. It will be seen that $\varepsilon_{obs.}$ is always somewhat smaller than $\varepsilon_{calc.}$ on this basis and that the ratio $\varepsilon_{obs.}/\varepsilon_{calc.}$ decreases with n. Nevertheless, the agreement is very satisfactory considering the approximate method of estimating a; some reasons for the discrepancies are further considered below.

Calculated and observed molecular-extinction coefficients for polyenes and polycyclic hydrocarbons.

$\varepsilon_{calc.}^{(1)} = 1{\cdot}31 \times 10^{20}\,r$. $\varepsilon_{calc.}^{(2)} = 1{\cdot}74 \times 10^{20}\,n$ for polyenes and polycyclic hydrocarbons, $\varepsilon_{calc.}^{(2)} = 1{\cdot}74 \times 10^{20}\,(n+1)$ for diphenylpolyenes.

	$\varepsilon_{obs.}$	r, A.[1]	$\varepsilon_{calc.}^{(1)}$.	$\varepsilon_{obs.}/\varepsilon_{calc.}^{(1)}$.	$\varepsilon_{calc.}^{(2)}$.	$\varepsilon_{obs.}/\varepsilon_{calc.}^{(2)}$.
		H·[CH = CH]$_n$·H.				
$n = 1$	15,000 [3]	1·35	17,400	0·86	17,400	0·86
2	21,000 [3]	3·66	48,000	0·44	34,800	0·60
3	53,000 [4]	6·14	81,000	0·65	52,200	1·01
4	64,000 [3]	8·62	113,000	0·57	69,600	0·92
5	51,000 [3]	11·10	145,000	0·34	87,000	0·59
6	70,000 [3]	13·6	178,000	0·39	104,000	0·67
11	65,000 [3]	26·0	340,000	0·19	191,000	0·34
		Ph·[CH = CH]$_n$·Ph.				
$n = 1$	27,000 [4]	3·68	47,000	0·57	34,800	0·78
2	41,000 [4]	6·16	81,000	0·51	52,200	0·78
3	65,000 [4]	8·64	114,000	0·57	69,600	0·93
4	90,000 [4]	11·1	145,000	0·62	87,000	1·03
5	94,000 [4]	13·6	178,000	0·53	104,000	0·90
6	117,000 [4]	16·1	210,000	0·56	122,000	0·96
7	135,000 [4]	18·6	242,000	0·56	139,000	0·97
Benzene ($n = 3$)	46,000 [3]	—	106,000	0·44	52,200	0·88
Naphthalene ($n = 5$)	133,000 [3]	—	176,000	0·76	104,000	1·28
Anthracene ($n = 7$) ...	180,000 [3]	—	248,000	0·72	122,000	1·50
Naphthacene ($n = 9$)...	180,000 [4]	—	320,000	0·56	157,000	1·14

[1] Bayliss, *J. Chem. Physics*, 1948, **16**, 287. [2] Platt, Klevens, and Price, *ibid.*, 1949, **17**, 466. [3] Data taken from Braude, *Ann. Reports*, 1945, **42**, 105. The data for $n > 3$ refer to alkyl-substituted polyenes. [4] Hausser, Kuhn, and Smakula, *Z. physikal. Chem.*, 1935, **29**, *B*, 385. [5] Mayneord and Roe, *Proc. Roy. Soc.*, 1935, **152**, *A*, 299. [6] Klevens and Platt, *J. Chem. Physics*, 1949, **17**, 470.

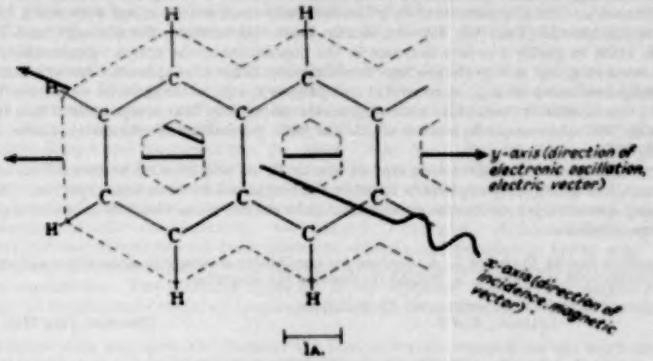
In the diphenyl polyenes, the total area containing π-electrons is increased by the terminal phenyl groups, but it is reasonable to assume that transitions involving the polyene chain will only be produced by photons striking the central, acyclic part of the molecule, whereas in the region of the phenyl groups the interaction probability for such transitions will be small. (This is in agreement with molecular-orbital calculations which indicate that the effective length of the conjugated system corresponds to the acyclic portion, cf. Bayliss, *loc. cit.*) Thus, for calculating extinction coefficients of the high-intensity, long-wave-length bands of the diphenylpolyenes, the chromophore area can be taken as approximately the same as for the corresponding unsubstituted polyenes with one extra ethylenic group. The values thus obtained (see Table) are in good agreement with those observed, the ratio $\varepsilon_{obs.}/\varepsilon_{calc.}$ falling consistently within the range 0·5—0·6 for $n = 1$—7.

Benzene exhibits three absorption bands, near 2550, 2000, and 1800 A., ascribed to transitions involving the system of π-electrons. The first two of these are of relatively low intensity and are assigned to "forbidden" transitions, but the 1800 A.-band is of high intensity and must be due to an "allowed" transition (Platt and Klevens, *Chem. Reviews*, 1947, **41**, 301; *J. Chem.*

Physics, 1948, **16**, 832; 1949, **17**, 470; Platt, *ibid.*, p. 484). Similar high-intensity bands of increasing wave-lengths and intensities are exhibited by the higher polycyclic hydrocarbons, and with the first three or four members of the series, the extinction coefficients are approximately proportional to the number of carbon atoms. This means that, as in the acyclic polyenes, the chromophore area also increases approximately linearly with the size of the molecule and indicates that the effective direction of incidence of the light absorbed is at right angles to the plane of the rings, and hence that the electric vector of the transitions lies in the plane of the rings (Fig. 3). This is in agreement with molecular-orbital theory (cf. Coulson, *loc. cit.*), and the same has been shown experimentally to apply to the low-intensity bands (Krishnan, *Proc. Indian Acad. Sci.*, 1938, **8**, 487; Scheibe, *Naturwiss.*, 1939, **8**, 478; Scheibe, Hartwig, and Müller, *Z. Elektrochem.*, 1943, **49**, 372). Since the π-electrons are equally distributed over all six carbon–carbon bonds, the chromophore area of benzene will therefore be approximately six times as great as that of ethylene, if any effect due to the thinning-out of the electron density is neglected. Similarly, for the higher members, the chromophore area and $\epsilon_{max.}$ will, on this basis, be equal to that of the acyclic polyene with the same number of carbon atoms. As before, the agreement between $\epsilon_{calc.}$ and $\epsilon_{obs.}$ is quite satisfactory (see Table). The calculated values are larger than those observed by factors up to about 2. Molecular-orbital calculations for this type of molecule, on the other hand, predict intensities which are smaller than those observed by factors of the order of 10 (Coulson, *Proc. Physical Soc.*, 1948, **60**, 257).

FIG. 3.

Absorption of light by benzenoid hydrocarbons (allowed electronic transition).



In the preceding discussion of acyclic and cyclic polyenes, the chromophore area has been taken to be proportional to the total number of carbon–carbon bonds in the polyene chain. This involves the assumption that the partial double-bond character of the conventional single carbon–carbon bonds is sufficient to render them as effective as the conventional double bonds for interaction with photons giving rise to π-electron transitions, and, similarly, that the " thinning-out " of the π-electron cloud will not appreciably reduce the effectiveness of the conventional double bonds for interaction with photons. The extent to which these assumptions are justified will depend on the exact relationship between π-electron density and interaction probability, concerning which little is known. An alternative approximation to the above is to assume that the effective chromophore area will be proportional to the *total* π-electron density, *i.e.*, to the number (**n**) of conventional ethylenic bonds. On this basis, ε should by (3a) also be directly proportional to **n**, and $\epsilon_{calc.} = 0{\cdot}87 \times 10^{20} a_{(ene)} \times n$, where $a_{(ene)}$ is the chromophore area of an ethylenic bond, *i.e.*, $\epsilon_{calc.} = 0{\cdot}87 \times 2 \times 10^{20} n = 1{\cdot}74 \times 10^{20} n$. The values thus obtained are in better agreement with the experimental data than those calculated previously in the case of the acyclic polyenes, but in less good agreement in the case of the aromatic hydrocarbons (see Table). This indicates that the " thinning-out " effect is more important in the acyclic than in the cyclic series, in agreement with the fact that the effective classical oscillator-strengths per π-electron are also consistently lower in polyenes than in aromatic hydrocarbons (Klevens and Platt, *J. Chem. Physics*, 1949, **17**, 470).

The fact that the observed and calculated values of ε are in fair agreement shows that the assumption made in deriving equation (3a), namely that the interaction probability is approximately unity for allowed transitions, is justified. For forbidden transitions, the interaction coefficient κ will be small and can readily be calculated from the experimental data by means of equation (3). This also provides a useful criterion of whether a transition is allowed or forbidden. Thus for the 2550-A. band of benzene, $\varepsilon_{obs.} = 200$ and $\varepsilon_{calc.} \sim \kappa \times 100{,}000$ (cf. Table), hence $\kappa = 0{\cdot}002$.

In conclusion, some other factors likely to be responsible for relatively small discrepancies between $\varepsilon_{calc.}$ and $\varepsilon_{obs.}$ may be briefly discussed. The data in the Table show that, even for the highest-intensity electronic bands, the observed extinction coefficients are generally slightly lower than those calculated by chromophore-area theory. This is not unexpected in view of the approximations made. In the first place, χ in equation (3) will generally be less than unity since polyatomic molecules usually occupy a number of vibrational levels in the ground state and consequently give rise to an absorption band of considerable width rather than an absorption line. This factor could be accounted for by comparing band areas ($\int \varepsilon dv$) rather than extinction coefficients (cf. Mulliken, *loc. cit.*) but the correction is not worth making as the data at present available for $\int \varepsilon dv$ are generally less accurate than the values of ε calculated by (3a). Secondly, apart from the intrinsic uncertainty in estimating the dimensions of the π-electron cloud, the effective chromophore area a will generally be smaller than that deduced by the simple considerations outlined above owing to intramolecular shielding effects. These are not easily amenable to quantitative treatment, but a qualitative indication of such effects is provided by the fact that $\varepsilon_{obs.}$ decreases with increasing substitution in the alkylated olefins (Klevens and Platt, *loc. cit.*). The decrease in absorption intensity usually associated with steric hindrance has been interpreted (Part VI, Braude, Koch, Jones, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890) as partly due to a decrease in the population of the active vibrational levels, *i.e.* to a decrease in χ, but it is probable that shielding effects are also operative in such cases. The abnormally low value of $\varepsilon_{obs.}$ in some natural polyenes, *e.g.*, γ-carotene ($n = 11$, see Table) is probably due to similar causes and also suggests the possibility that compounds of this type may not possess the all-*trans*-configuration which has been postulated (Zechmeister, *Chem. Reviews*, 1944, **34**, 267).

Chromophore area considerations are, of course, in no way limited to transitions involving π-electrons, but are equally applicable to other electronic and to vibrational spectra. However, hardly any quantitative extinction measurements in the far ultra-violet or infra-red regions are at present available.

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85. *Cinnolines. Part XXV. Experiments with 3-Halogeno-4-hydroxycinnolines. Some Halogen Exchange Reactions.*

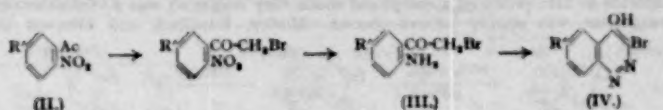
By K. SCHOFIELD and T. SWAIN.

The bromination of diazotised *o*-aminoacetophenone, and the bromination and chlorination of 4-hydroxycinnoline, have given mediocre yields of 3-halogeno-4-hydroxycinnolines. The substitution of bromine by chlorine which occurs when bromo-4-hydroxycinnolines react with phosphorus chlorides appears to proceed by different mechanisms, depending on the presence of the bromine at $C_{(3)}$ or $C_{(4)}$. Qualitative comparison with related 4-hydroxyquinolines shows that these undergo chlorination and bromination more rapidly and more efficiently at $C_{(3)}$ than do analogous cinnolines, but halogen exchange reactions occur much more slowly, if at all.

THE synthesis of some 3-halogeno-4-hydroxycinnolines (I; R = Cl or Br, R′ = H, Cl or Br) was recently reported (Schofield and Simpson, *J.*, 1948, 1170). Some experiments with these compounds and a qualitative comparison with analogous quinoline derivatives are now described.

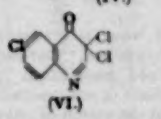
The original synthesis of 3-bromo-4-hydroxycinnolines (II ⟶ IV) suffers from the disadvantages, especially in the case of (II; R′ = H), that pure nitroacetophenones are essential, and that compounds (III) are unstable. Thus, before beginning a study of 3-bromo-

4-hydroxycinnolines, some experiments were made in search of a simplified route to these compounds. The results are of interest, but it cannot be claimed that the desired products have been rendered any easier of access.



(II.) (III.) (IV.)

(I.) (V.)



(VI.)

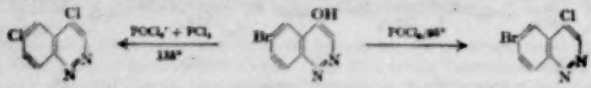
Bülow and Schmachtenberg (*Ber.*, 1908, **41**, 2607) found that the decomposition of benzenediazonium perbromide in the presence of acetophenone gave ω-bromoacetophenone, and Hopf and Le Fèvre (*J.*, 1939, 1067) also observed the brominating action of a compound of this type. It seemed possible, therefore, that decomposition of the perbromide from diazotised *o*-aminoacetophenone might provide 3-bromo-4-hydroxycinnoline, obviating the need for pure *o*-nitroacetophenone, *o*-aminoacetophenone being available from the crude nitro-compound arising from the nitration of acetophenone (Schofield and Swain, *J.*, 1948, 384). Under a variety of conditions 3-bromo-4-hydroxycinnoline was obtained by this method. In no case was the yield greater than 34%, but the experiments were not exhaustive and the reaction might repay further study.

Direct halogenation of the readily available 4-hydroxycinnolines promised to be an attractive route to 3-halogeno-4-hydroxycinnolines. Examples of analogous brominations of quinoline derivatives are mentioned in the early literature (Chick and Wilsmore, *J.*, 1910, **97**, 1990; Knorr, *Annalen*, 1886, **236**, 91; Meyer and Heinmann, *Compt. rend.*, 1936, **203**, 264), and recently Riegel and his co-workers (*J. Amer. Chem. Soc.*, 1946, **68**, 1229, 1532) prepared 3-bromo-4-hydroxyquinolines by this method, whilst Surrey and Cutler (*ibid.*, p. 2570) made a comprehensive study of the direct halogenation of ethyl 4-hydroxyquinaldates with sulphuryl chloride, bromine, and iodine monochloride, in acetic acid, obtaining the corresponding 3-halogeno-derivatives. Consequently, we treated 4-hydroxy-, 6-chloro-4-hydroxy-, and 6-bromo-4-hydroxy-cinnoline with both sulphuryl chloride and bromine in acetic acid. In no case was halogenation so rapid or so efficient as with the related quinoline derivatives under the same conditions. The products appeared to be mixtures, from which mediocre yields (*ca.* 20%) of 3-halogeno-4-hydroxycinnolines (I; R = Cl or Br; R′ = H, Cl or Br) were isolated.

For comparative purposes, and because the products were required for the work described later in this paper, the quinoline analogues (V; R = Cl or Br, R′ = H, Cl or Br) of the above cinnolines were prepared. 4-Hydroxy- and 6-chloro-4-hydroxy-quinoline are readily prepared by the ethoxymethylenemalonic ester reaction (see, among others, Price and Roberts, *ibid.*, p. 1204) and we have now prepared *6-bromo-4-hydroxyquinoline* by this method (see Experimental). By the action of sulphuryl chloride on 4-hydroxyquinoline we isolated a low yield of a trichloro-derivative (cf. Riegel *et al.*, *ibid.*, p. 1229). Surprisingly, this compound appeared to be converted by mixed phosphorus chlorides into a trichloroquinoline which did not depress the m. p. of 3 : 4 : 6-trichloroquinoline (see below). Although mixed m. p.s are not reliable with compounds of this type, the sequence of reactions suggests some such structure as (VI) for the initial product. With 6-chloro- and 6-bromo-4-hydroxyquinoline (in contrast to the cinnoline derivatives), sulphuryl chloride effected rapid and efficient monochlorination, giving what we regard as 3 : *6-dichloro-* and 3-*chloro-6-bromo-4-hydroxyquinoline*. Bromination of the hydroxy-compounds under the conditions of Surrey and Cutler (*loc. cit.*) (Riegel *et al.*, *loc. cit.*, used a longer reaction time) proceeded rapidly enough at 95° to give good yields of 3-*bromo-*, 6-*chloro*-3-*bromo-*, and 3 : 6-*dibromo-4-hydroxyquinoline* in ten minutes.

One of our objects in preparing the above halogeno-4-hydroxycinnolines was to examine further the problem of halogen exchange. In previous cinnoline studies (Schofield and Simpson, *loc. cit.*; Atkinson and Simpson, *J.*, 1947, 232; Keneford, Morley, and Simpson, *J.*, 1948, 1702) cases of the replacement of a bromine atom by a chlorine atom in the diazonium salt stage of the Borsche synthesis have been observed. But another type of replacement involving a

bromine atom in a cinnoline nucleus was observed by Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 419), who noticed that, although phosphorus oxychloride at 95° converted 6-bromo-4-hydroxycinnoline into 4-chloro-6-bromocinnoline, a mixture of phosphorus oxychloride and pentachloride at 135° produced a compound which they suggested was 4 : 6-dichlorocinnoline. This suggestion was readily proved correct. Morley, Keneford, and Simpson (*loc. cit.*)



observed what is probably a similar replacement of the nitro-group in 7-chloro-6-nitro-4-hydroxycinnoline. Our own interest in reactions of this sort was prompted by the observation that mixed phosphorus chlorides converted 3-bromo-4-hydroxycinnoline into a product intermediate in composition between 4-chloro-3-bromo- and 3 : 4-dichloro-cinnoline. We have examined the action of phosphorus oxychloride and pentachloride, alone and mixed, at 95° and 135°, on 3-bromo-, 6-bromo-, 6-chloro-3-bromo-, and 3 : 6-dibromo-4-hydroxycinnoline.

Three criteria were used to detect and roughly estimate the occurrence of bromine replacement by chlorine. Most important was elementary analysis of the products, and of the derived 4-phenoxy-compounds. Secondly, although with these compounds mixed m. p.s are of little value since depressions are not in general observed, yet m. p.s of the products provided a useful criterion since it was found that they rose as the degree of exchange decreased. In this connection 4 : 6-dichloro- and 4-chloro-6-bromo-cinnoline, required as standard substances, were already known (Keneford and Simpson, *J.*, 1947, 917; Leonard and Boyd, *loc. cit.*), and by usual methods we prepared 3 : 4-*dichloro-* and 3 : 4 : 6-*trichloro-cinnoline*, and also 3-*chloro*-4-*phenoxycinnoline*. Thirdly, if replacement was occurring, bromine appeared in the reaction vessel.

The essential results, obtained under the standard conditions used in these experiments, are summarised in Table I, from which the degree of exchange in any example can be judged roughly by the m. p. of the product, and also by the approximate calculation of percentage exchange based on the carbon content of the compounds.

It was important to decide if the 4-hydroxy-group was involved in the exchange reaction, or if its replacement by chlorine was completed before substitution of bromine by chlorine occurred. The latter possibility seemed the more likely since Leonard and Boyd (*loc. cit.*) reported that the hydroxyl group of 4-hydroxycinnoline was replaced in five minutes under the action of phosphorus oxychloride, and Surrey and Cutler (*loc. cit.*) have shown that in ten minutes the same reagent can convert many 4-hydroxyquinolines into the 4-chloro-compounds. We find that 4-chloro-, 4 : 6-dichloro-, and 3 : 4-dichloro-cinnoline are formed quantitatively in this short reaction time, and by this means it was possible to convert bromine-containing 4-hydroxycinnolines into the 4-chloro-compounds with a minimum of halogen exchange, although the products were not quite pure. Complete proof that the 4-hydroxy-group is not essential to the exchange reaction was provided by showing that further treatment of these fairly pure 4-chloro-bromocinnolines with phosphorus chlorides caused exchange of chlorine for bromine in the same way as when the 4-hydroxy-compounds were used in the reaction.

The quinoline derivatives described above provided an interesting comparison with their cinnoline analogues, when treated under the conditions which caused halogen exchange in the latter. 4 : 6-Dichloro- and 4-chloro-3-bromo-quinoline have been described by Riegel *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1264, 1229), and we have now prepared 4-*chloro*-6-*bromo-*, 3 : 4 : 6-*trichloro-*, 3 : 4-*dichloro*-6-*bromo-*, 4 : 6-*dichloro*-3-*bromo-*, and 4-*chloro*-3 : 6-*dibromo-quinoline*. Treatment of the bromine-containing compounds with phosphorus chlorides, under conditions which replace, partly or completely, the bromine in the cinnoline analogues, did cause some halogen exchange (as evinced by bromine vapour appearing in the reaction vessels) but analysis showed it to have occurred to a very small extent. This was expected in view of earlier reports of the preparation of 4-chloro-compounds from bromine-substituted 4-hydroxyquinolines. Thus, Kermack and Weatherhead (*J.*, 1939, 563) boiled 6-bromo-4-hydroxyquinaldine for four hours with phosphorus oxychloride without apparently replacing the bromine atom. Steck and his co-workers (*J. Amer. Chem. Soc.*, 1946, **68**, 129, 380) satisfactorily prepared 4-chloro-5-, -6-, and -7-bromo-3-methylquinoline by a similar method, and Riegel *et al.* (*loc. cit.*) likewise obtained 4-chloro-3-bromoquinoline.

The conclusions to be drawn from Table I and from the above discussion can be stated briefly: (i) Replacement of the 4-hydroxy-group precedes halogen exchange and is indeed a very

TABLE I.

Summary of results obtained in halogen exchange reactions.

Conditions.				M. p.[a] and exchange, % of products from substituted 4-hydroxycinnoline.							
				6-Bromo-.		3-Bromo-.		6-Chloro-3-bromo-.		3 : 6-Dibromo-.	
Reagent.[b]	Time (hrs.).	Temp.	Reflux or open.[c]	M. p.	Exchange, %	M. p.	Exchange, %	M. p.	Exchange, %	M. p.	Exchange, %[d]
M	2	95°	O	113°	—	147°[e]	34	142-5°	100	148°	47
M	½	95	O	126	—	—	—	—	—	—	—
M	2	95	R	—	—	143-5°[e]	37	143-5[f]	83	147	47
M	2	135	O	113°[g]	100[h]	149-5	7·5	149-5	51	156-5	31
M	2	135	R	—	—	153	6	154-5	14	161	10
M	24	95	R	—	—	130	—	—	—	—	—
M	24	135	R	—	—	143	—	148	—	152	—
O	2	95	R	118	—	142	—	145	—	148	—
O	2	135	R	113	—	151-5	—	152	—	159	—
P	1	95	R	126	—	127	—	140	—	—	—
P	½	135	R	—	—	130	—	135	—	141	—

(*a*) M. p.s of possible products: **3** : 4-dichlorocinnoline, m. p. 126—127°; **4** : 6-dichlorocinnoline, m. p. 112—113°; **3** : **4** : 6-trichlorocinnoline, m. p. 141—142°. (*b*) M = mixed phosphorus chlorides; P = phosphorus pentachloride; O = phosphorus oxychloride. (*c*) R = reflux; O = open vessel. (*d*) Based on total bromine (2 atoms). (*e*) This is the only case where reaction under reflux caused more exchange, but the difference is small. (*f*) 1 hour's heating. (*g*) ½ hour or 2 hours. (*h*) From Leonard and Boyd's figures (*loc. cit.*).

rapid reaction. (ii) A mixture of phosphorus oxychloride and pentachloride being used, replacement of the bromine at $C_{(4)}$ is relatively rapid, and occurs more readily at the higher of the two temperatures used. (iii) By comparison, replacement of a bromine atom at $C_{(6)}$ is relatively slow, appears to be encouraged by the presence of a halogen atom at $C_{(3)}$, and is more rapid at 95° than at 135°. (iv) Replacement of bromine, whether at $C_{(3)}$ or $C_{(6)}$, by using phosphorus pentachloride, proceeds more rapidly at the higher temperature. (v) Phosphorus oxychloride, in contrast, produces similar results to those obtained with the mixed chlorides. (vi) Generally, use of an open vessel, whence bromine can easily escape, facilitates exchange, and the reverse is true for reactions carried out under reflux. (vii) Halogen exchange in the quinoline series proceeds very much more slowly, if at all appreciably, than in the cinnoline series.

Useful discussion of these results is rendered difficult, first by the absence of true analogies, and secondly by ignorance of the mechanism of reactions between phosphorus chlorides and compounds of the present type. Several examples of the replacement of bromine atoms by chlorine, through the agency of phosphorus pentachloride, in both the benzene and the naphthalene series have been reported (Schmidt and Wagner, *Annalen*, 1912, **387**, 164; Cone and Robinson, *Ber.*, 1907, **40**, 2160; Sindall, *Chem. News*, 1890, **60**, 58), but the conditions have usually been comparatively severe. In any case, different mechanisms may be involved in these examples. At first it seemed possible that the 4-hydroxy-group might be intimately connected with exchange of the 3-bromo-atom, somewhat in the manner in which a hydroxyl group adjacent to a halogen atom in a naphthalene compound controls the subsequent mode of halogenation (Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 245), but the facts presented make it clear that the hydroxyl group is in no way involved in the reaction.

The different form of temperature dependence of the substitution at $C_{(4)}$ as against $C_{(3)}$ seems to suggest that different mechanisms of replacement are operative at each position. Possibly replacement of the 6-bromo-atom is an ordinary nucleophilic substitution, and from the point of view of comparative heterocyclic chemistry it is interesting that the cinnoline compounds are more susceptible to nucleophilic replacement than are the members of the quinoline series.

The qualitative results of bromination and chlorination of 4-hydroxycinnolines and 4-hydroxyquinolines suggest, on the other hand, that in the quinoline compounds $C_{(3)}$ is more readily attacked by electrophilic reagents than $C_{(6)}$ in 4-hydroxycinnolines. This is also true of our observation that 4-hydroxycinnoline fails to partake in a Mannich reaction under conditions which produce substitution of this kind in 4-hydroxyquinoline derivatives (Price and Jackson, *J. Amer. Chem. Soc.*, 1946, **68**, 1282). It should be noted that our results do not allow us to decide if $C_{(3)}$ in 4-hydroxyquinolines is absolutely more susceptible to electrophilic substitution than $C_{(6)}$ in 4-hydroxycinnolines, or only relatively so, as compared with other positions in the

two nuclei. Only a knowledge of the fate of material not accounted for as 3-halogeno-4-hydroxycinnoline, *i.e.*, whether it remained unsubstituted or whether substitution occurred at positions other than $C_{(8)}$, could decide this question.

It would clearly be of interest to examine the ease of halogen exchange in cinnolines unsubstituted at $C_{(8)}$ and this we hope to do.

Experimental.

(M. p.s are uncorrected.)

Bromination of Diazotised o-Aminoacetophenone.—(i) The amine (1 g.) in sulphuric acid (10 c.c.; 60% v/v) was diazotised at 0° with aqueous sodium nitrite (10%), and a solution of potassium bromide (1·47 g.) and potassium bromate (0·41 g.) in water (10 c.c.) added slowly at −5° to 0°. The suspension of brown granular solid produced was left overnight and then warmed at 80° for ½ hour, and the tarry resin formed crystallised twice from alcohol. 3-Bromo-4-hydroxycinnoline (0·25 g., 15%) was thus isolated as pale brown needles, m. p. 273—274°, alone and mixed with an authentic specimen (m. p. 275—276°).

(ii) *o*-Aminoacetophenone (0·5 g.) was treated as in (i) but the suspension was left for 1 week at room temperature before being worked up as before. There resulted 0·28 g. (34%) of 3-bromo-4-hydroxycinnoline, m. p. 271—272°.

(iii) The ketone (0·59 g.) was diazotised as before, treated with a solution of potassium bromide (1·18 g.) and potassium bromate (0·21 g.) in water (5 c.c.), and worked up as in (ii), yielding 20% of the desired product.

(iv) The amine (1 g.) was diazotised and treated with a solution of potassium bromide (1·24 g.) and bromine (2·04 g.) in water (10 c.c.), left overnight, and worked up as in (i), yielding 12·5% of 3-bromo-4-hydroxycinnoline.

Direct Halogenation of 4-Hydroxycinnolines.

Chlorination of 4-Hydroxycinnoline.—The cinnoline (0·5 g.) in acetic acid (20 c.c.) and acetic anhydride (1 c.c.) was warmed at 95° for 4 hours with sulphuryl chloride (0·51 g.), the mixture refluxed for 5 minutes and then cooled, sodium hydroxide (0·2 g.) in water (10 c.c.) added, and the solution left at 0° for 3 hours. Recrystallisation of the precipitate (0·24 g.; m. p. 262—263°) from acetic acid gave 3-chloro-4-hydroxycinnoline (0·14 g., 22%), m. p. 278—279°, alone and mixed with an authentic specimen (m. p. 278—279°). Acetylation with boiling acetic anhydride gave a derivative, m. p. 124—125°, which did not depress the m. p. (124—125°) of genuine 3-chloro-4-acetoxycinnoline.

Chlorination in boiling acetic acid for 4 hours gave the same result, but one experiment at 95° using only 2 drops of acetic anhydride gave none of the chlorocinnoline.

Chlorination of 6-Chloro-4-hydroxycinnoline.—The cinnoline (0·5 g.), acetic acid (20 c.c.), acetic anhydride (1 c.c.), and sulphuryl chloride (0·42 g.) were refluxed together for 4 hours and worked up as above. The product (0·19 g., 32%), m. p. 301—303°, and its acetyl derivative, m. p. 148—149°, were identical with 3 : 6-dichloro-4-hydroxycinnoline (m. p. 302—303°) and 3 : 6-dichloro-4-acetoxycinnoline (m. p. 149—150°), respectively.

Chlorination of 6-Bromo-4-hydroxycinnoline.—By the same method 6-bromo-4-hydroxycinnoline (0·5 g.) gave 22% of 3-chloro-6-bromo-4-hydroxycinnoline, m. p. 306—307°, giving no depression on admixture with a pure specimen, m. p. 309—310°.

Bromination of 4-Hydroxycinnoline.—4-Hydroxycinnoline (1 g.), acetic acid (20 c.c.), and bromine (1·15 g.) were warmed at 95° for 2½ hours, crystals appearing after ½ hour. After removal of the solvent under reduced pressure the residue (hydrobromides) was triturated with dilute ammonia solution, leaving a white solid (1·17 g.), m. p. 235—237°. Neutralisation of the ammoniacal washings with acetic acid gave some impure starting material (0·04 g.). Three crystallisations of the product from ethanol gave substantially pure 3-bromo-4-hydroxycinnoline (0·31 g., 20%), m. p. 272—273° showing no depression on admixture with a pure specimen, m. p. 275—276°. The acetyl derivative, m. p. 139—140°, was also identical with 3-bromo-4-acetoxycinnoline, m. p. 139—140°.

Bromination in boiling acetic acid during 1 hour gave 15% of 3-bromo-4-hydroxycinnoline.

Bromination of 6-Chloro-4-hydroxycinnoline.—The cinnoline (1 g.), treated as above, provided after trituration with ammonia a white solid (1·18 g., m. p. 275—276°). Four crystallisations from alcohol gave white needles (0·28 g., 19·5%), m. p. 308—309°, alone and mixed with genuine 6-chloro-3-bromo-4-hydroxycinnoline, m. p. 310—311°. The acetyl derivative, m. p. 165—166°, was identical with 6-chloro-3-bromo-4-acetoxycinnoline, m. p. 166—167°.

Bromination of 6-Bromo-4-hydroxycinnoline.—A white solid (1·02 g.; m. p. 275—277°) was obtained by brominating 6-bromo-4-hydroxycinnoline in the same way as above and triturating the product with ammonia. Four crystallisations from alcohol gave white needles (0·30 g., 22%), m. p. 313—314° (acetyl derivative, m. p. 178—179°), identical with 3 : 6-dibromo-4-hydroxycinnoline, m. p. 315—316° (acetyl derivative, m. p. 179—180°).

Halogenated 4-Hydroxyquinolines.

6-*Bromo*-4-*hydroxyquinoline.*—(*a*) *p*-Bromoaniline (25·2 g.) and ethyl ethoxymethylenemalonate (32 g.) (Fuson, Parham, and Reed, *J. Org. Chem.*, 1946, **11**, 194) were heated at 95° for 2 hours, and the alcohol formed was removed under reduced pressure. One crystallisation from methanol gave pale yellow crystals of a product suitable for further use (46 g.; m. p. 98—99°), and further crystallisation gave stout white needles of *ethyl β-(p-bromoanilino)-α-carbethoxyacrylate*, m. p. 100—101° (Found: C, 49·4; H, 4·75. $C_{14}H_{16}O_4NBr$ requires C, 49·1; H, 4·7%).

(*b*) The above compound (40 g.), finely powdered, was added during 10 minutes to boiling diphenyl ether (400 g.), and the mixture refluxed for ½ hour. After the mixture had cooled, ligroin was added (400 c.c.), and the product collected, washed with more ligroin and some ether, and dried, yielding pure

ethyl 6-bromo-4-hydroxyquinoline-3-carboxylate (24 g., 99%). It formed lustreless white microcrystals (from alcohol), m. p. 286—287° (Found: C, 49·8; H, 3·5. $C_{12}H_{10}O_3NBr$ requires C, 48·7; H, 3·4%).

(*c*) The ester (30 g.) was refluxed with potassium hydroxide solution (250 c.c.; 10%) for 2 hours, and the solution filtered (charcoal) and acidified with concentrated hydrochloric acid. The precipitate (22·7 g., 84%) of almost pure *4-hydroxyquinoline-3-carboxylic acid* separated from alcohol in white microcrystals, m. p. 271° (decomp.) (Found: C, 45·5; H, 2·3. $C_{10}H_6O_3NBr$ requires C, 44·8; H, 2·3%).

(*d*) The acid (5 g.) was added to boiling diphenyl ether (25 g.) during 5 minutes, the mixture was boiled under reflux for 25 minutes, cooled, and diluted with ligroin (25 c.c.), and the precipitate collected and washed with ligroin and ether. The substantially pure product (4·02 g.) formed stout pale yellow needles of *6-bromo-4-hydroxyquinoline*, m. p. 282—283°, from alcohol (Found: C, 46·3; H, 3·0. $C_9H_6ONBr,\frac{1}{2}H_2O$ requires C, 46·4; H, 3·0%).

A similar result was obtained by heating the acid at 285° for ½ hour, but the initial product was not so pure as that obtained by the first method.

Chlorination of 4-Hydroxyquinoline.—4-Hydroxyquinoline (1 g.) in acetic acid (3·2 c.c.) and acetic anhydride (0·8 c.c.) at 45° was added to sulphuryl chloride (1·05 g.). The mixture was kept at the same temperature for 25 minutes, boiled for 5 minutes, and diluted with water (6 c.c.). The white solid (0·57 g.; m. p. 270—280°) was digested with alcohol (40 c.c.), and the residue (0·24 g.; m. p. >300°) crystallised from alcohol, giving white lustreless microcrystals of a *compound*, m. p. >320° (Found: C, 42·1; H, 2·2. $C_9H_5ONCl_2$ requires C, 43·5; H, 1·6%).

3: *6-Dichloro-4-hydroxyquinoline.*—6-Chloro-4-hydroxyquinoline (1·64 g.) in acetic acid (9 c.c.) and acetic anhydride (1 c.c.) was added to sulphuryl chloride (1·37 g.) at 45°. There was an immediate reaction and the temperature rose to >100°. The mixture was kept at 60—65° for ½ hour, boiled for 5 minutes, and then cooled, and sodium hydroxide (0·4 g.) in water (6 c.c.) added. Recrystallisation of the almost pure product (1·38 g.) from acetic acid gave lustreless yellow microcrystals of **3**: *6-dichloro-4-hydroxyquinoline*, m. p. >320° (Found: C, 50·6; H, 2·5. $C_9H_5ONCl_2$ requires C, 50·5; H, 2·4%).

3-Chloro-6-bromo-4-hydroxyquinoline.—6-Bromo-4-hydroxyquinoline (1·3 g.) was chlorinated as above, but after addition to sulphuryl chloride (0·87 g.) the mixture was kept at 100° for ½ hour. The product (1·14 g.) formed white microcrystals of *3-chloro-6-bromo-4-hydroxyquinoline*, m. p. >320°, from acetic acid (Found: C, 41·8; H, 2·3. $C_9H_5ONClBr$ requires C, 41·6; H, 1·95%).

3-Bromo-4-hydroxyquinoline.—Addition of bromine (0·72 c.c.) to 4-hydroxyquinoline (2 g.) in acetic acid (6 c.c.) at 70° caused an immediate reaction, the temperature rising to >100°. After 10 minutes at 70° the solution was cooled, and sodium hydroxide (0·55 g.) in water (10 c.c.) added, yielding a white solid (3·03 g.; m. p. 272—274°). Crystallisation from alcohol gave white microcrystals of 3-bromo-4-hydroxyquinoline (2·43 g., 79%), m. p. 281—282° (Riegel *et al.*, *loc. cit.*, give m. p. 288—289°, yield 89%).

6-Chloro-3-bromo-4-hydroxyquinoline.—The quinoline (2 g.), acetic acid (6 c.c.), and bromine (0·6 c.c.) were heated at 95° for 10 minutes, much solid being quickly deposited. Worked up as above, the mixture gave a white solid (2·4 g.) which separated from acetic acid as dull buff microcrystals of *6-chloro-3-bromo-4-hydroxyquinoline*, m. p. >320° (Found: C, 42·4; H, 2·2. $C_9H_5ONClBr$ requires C, 41·6; H, 1·95%).

3: *6-Dibromo-4-hydroxyquinoline.*—6-Bromo-4-hydroxyquinoline (2 g.), treated as above (0·5 c.c. of bromine), gave a pale yellow solid (2·51 g.) which separated from acetic acid as pale yellow microcrystals of **3**: *6-dibromo-4-hydroxyquinoline*, m. p. >320° (Found: C, 35·9; H, 1·7. $C_9H_5ONBr_2$ requires C, 35·7; H, 1·7%).

Halogen Exchange Reactions and Related Experiments with Cinnoline Derivatives.

3: *4-Dichloro- and* **3**: **4**: *6-Trichloro-cinnoline.*—By the usual method (Keneford and Simpson, *loc. cit.*), 3-chloro- (1 g.) and **3**: 6-dichloro-4-hydroxycinnoline (0·4 g.) gave the desired products (0·7 g. and 0·3 g., respectively). **3**: *4-Dichlorocinnoline* formed white needles, m. p. 126—127°, from ether–ligroin (b. p. 60—80°) (Found: N, 14·8; Cl, 36·2. $C_8H_4N_2Cl_2$ requires N, 14·1; Cl, 35·6%), and **3**: **4**: *6-trichlorocinnoline* gave pale yellow needles, m. p. 141—142°, from the same solvent (Found: C, 41·2; H, 1·2; Cl, 45·9. $C_8H_3N_2Cl_3$ requires C, 41·15; H, 1·3; Cl, 45·6%).

3-Chloro-4-phenoxycinnoline.—**3**: 4-Dichlorocinnoline (1·5 g.) was converted by standard means (Keneford and Simpson, *loc. cit.*) into *3-chloro-4-phenoxycinnoline* (1·74 g.), which formed white needles, m. p. 120—121°, from ether–ligroin (b. p. 60—80°) (Found: C, 64·7; H, 3·9; N, 10·9. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9%).

Action of Mixed Phosphorus Chlorides on Bromo-4-hydroxycinnolines.—The experiments with 3-bromo-4-hydroxycinnoline are described in some detail and serve as a model for those with other compounds, indicating the sort of yield obtained in these reactions. The products from 3-bromo-4-hydroxycinnoline are described in Table II (A), and those obtained under similar conditions from 6-bromo-, 6-chloro-3-bromo-, and **3**: 6-dibromo-4-hydroxycinnoline, in Table II (B), (C), and (D), respectively. All the products were purified by crystallisation from ether–ligroin (b. p. 60—80°).

(i) 3-Bromo-4-hydroxycinnoline (0·5 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (5 c.c.) were heated at 95° for 2 hours in a short-necked flask fitted with a calcium chloride tube, and the mixture was decomposed with ice, basified (20% sodium hydroxide), and extracted with ether. The dried (Na_2SO_4) extract yielded a white solid (0·46 g.).

(ii) The cinnoline (0·4 g.) was treated in the same way, except that the flask was fitted with a water condenser. Yield: 0·38 g.

(iii) The cinnoline (0·4 g.) was treated as in (i), but at 135—140° for 2 hours, the flask being fitted with a short condenser so arranged that the refluxing vapours could just escape, the loss being made up by addition of phosphorus oxychloride from a tap funnel. Yield: 0·39 g.

(iv) The cinnoline (0·4 g.) was treated as in (iii), but under complete reflux. Yield: 0·38 g.

(v) 3-Bromo-4-hydroxycinnoline (0·2 g.) was treated as in (i), but for 24 hours. Yield: 0·19 g.

(vi) The hydroxycinnoline (0·2 g.) was treated as in (iv), but for 24 hours. Yield: 0·18 g.

TABLE II.

Conditions.	Product. M. p.[a]	Analysis, %. C.	H.	Possible product. Compound.	M. p.	Analysis, %. C.	H.
				(A)			
(i) *	146·5—147°	42·1	1·9	3 : 4-Dichlorocinnoline	126—127°	49·3	2·0
(ii) *	143—143·5	42·3	2·0				
(iii) *	148·5—149·5	39·95	1·75	4-Chloro-3-bromocinnoline	?	39·5	1·7
(iv) *, †	152·5—153	39·9	1·8				
(v) *	130—131	—	—				
(vi) *	145—144	—	—				
				(B)			
(i) *	112—113	—	—	4 : 6-Dichlorocinnoline	113—114[d]	—	—
(iv) *	112—113	—	—				
(i) For ½ hour	126—127	—	—	4-Chloro-6-bromocinnoline	126—127[d]	—	—
(iv) For ½ hour *	112—113	—	—				
				(C)			
(i) For 1 hour	142—142·5	41·7	1·85	3 : 4 : 6-Trichlorocinnoline	141—142	41·1	1·3
(ii) For 1 hour *, †	143—143·5	39·9	1·4				
(iii) *	149—149·5	37·6	1·7				
(iv) *, †	154—154·5	35·4	1·4	4 : 6-Dichloro-3-bromocinnoline	?	34·6	1·1
(vi) *	147—148	—	—				
				(D)			
(i) *, †	145·5—146	34·2	1·4	3 : 4 : 6-Trichlorocinnoline	141—142	41·4	1·3
(ii) *	146·5—147	34·2	1·4	4 : 6-Dichloro-3-bromocinnoline	?	34·6	1·1
(iii) *	156—156·5	32·6	1·7				
(iv) *, †	160·5—161	30·5	1·4	3 : 4-Dichloro-6-bromocinnoline	?	34·6	1·1
(vi) *	151—152	—	—	4-Chloro-3 : 6-dibromocinnoline	?	29·8	0·9

(*a*) Bromine was visible in the reaction vessel. (*b*) M. p.s are uncorrected. They were determined with an ordinary thermometer in a small oil-bath, the temperature being raised 1° per minute. Usually 3 specimens were examined at once. Mixtures of the products did not show depressions, but melted at an intermediate temperature. (*c*) These products were phenoxylated. See Table III. (*d*) Leonard and Boyd (*loc. cit.*) give m. p. 113—114° and 126—127°, respectively.

Phenoxylation of Products from Exchange Reactions.—The product (1 part) was heated with phenol (10 parts) at 180° for 2 hours, and the mixture cooled somewhat and poured into excess 5N-sodium hydroxide solution. Ether removed the derivative, which was isolated from the dried (Na_2SO_4) extract in an almost pure state (90—95% yield), and recrystallised from ether–ligroin (b. p. 60—80°), forming white or cream-coloured needles.

Action of Phosphorus Oxychloride on Bromo-4-hydroxycinnolines.—In each case the cinnoline (0·1 g.) and phosphorus oxychloride (2 c.c.) were heated at 95°, or at 135° under reflux, for 2 hours, and the products isolated and crystallised in the usual way. In conjunction with the above results the m. p.s of the products (see Table IV) serve to indicate the extent of halogen exchange.

Action of Phosphorus Pentachloride on Bromo-4-hydroxycinnolines.—An intimate mixture of the cinnoline (0·1 g.) and phosphorus pentachloride (1 g.) was heated, for either 1 hour at 95° or ½ hour at 140—150°, and worked up as before. The results are given in Table V.

Preparation of 4-Chlorocinnolines with Phosphorus Oxychloride.—The hydroxy-compound was refluxed with the oxychloride at 135—140° until a clear solution was obtained, and heating was then continued at 95° to a total of 10 minutes. The products (see Table VI) were isolated as before and crystallised once.

TABLE III.

Supposed 4-chloro-compound. Table II.	Compound.[a]	Product. M. p.	Analysis, %. C.	H.	Possible product. Compound.	Analysis, %. C.	H.
A (iv)	4-Chloro-3-bromocinnoline	143—144°	56·15	3·05	3-Bromo-4-phenoxycinnoline	55·8	3·0
C (ii)	3 : 4 : 6-Trichlorocinnoline	107—108	56·7	2·95	3 : 6-Dichloro-4-phenoxycinnoline	57·8	2·8
C (iv)	4 : 6-Dichloro-3-bromocinnoline	113—114	53·2	2·6	6-Chloro-3-bromo-4-phenoxycinnoline	50·1	2·4
D (i)	3 : 4-Dichloro-6-bromocinnoline	128—129	50·1	2·5	3-Chloro-6-bromo-4-phenoxycinnoline	50·1	2·4
D (iv)	4-Chloro-3 : 6-dibromocinnoline	135—136	46·7	2·5	3 : 6-Dibromo-4-phenoxycinnoline	44·1	2·1

(*a*) *I.e.*, the substance to which the analysis in Table II approximates most closely.

TABLE IV.

Compound.	Temp.	Crude product. Yield (g.).	M. p.	Recrystallised product. Yield (g.).	M. p.
3-Bromo-4-hydroxycinnoline	95°	0·08	136—138°	0·05	141—142°
	135	0·10	151—152	0·08	151—151·5
6-Bromo-4-hydroxycinnoline	95	0·09	116—117	0·04	117—118
	135	0·08	105—107	0·02	112—113
6-Chloro-3-bromo-4-hydroxycinnoline	95	0·09	143—145	0·05	144—145
	135	0·10	151—152	0·07	152—153
3 : 6-Dibromo-4-hydroxycinnoline [a]	95	0·05	141—143	0·04	147—148
	135	0·05	155—156	0·04	158—159

(*a*) 0·05 G. of hydroxy-compound used.

TABLE V.

Compound.	Temp.	Crude product. Yield (g.).	M. p.	Crystallised product. Yield (g.).	M. p.
3-Bromo-4-hydroxycinnoline	95°	0·10	121—123°	0·03	126—127°
	140	0·02	125—130	—	—
6-Bromo-4-hydroxycinnoline	95	0·05	123—125	0·02	125—126
6-Chloro-3-bromo-4-hydroxycinnoline	95	0·10	137—139	0·05	140—141
	140	0·02	132—135	—	—
3 : 6-Dibromo-4-hydroxycinnoline	140	0·04	131—133	0·01	140—141

TABLE VI.

Compound.	Wt., g.	$POCl_3$, c.c.	Time, mins. 140°.	95°.	Product. G.	M. p.	Recrystallised, m. p.
4-Hydroxycinnoline	0·2	0·6	½	9½	0·17	73—74°	76—77°
3-Chloro-4-hydroxycinnoline	0·1	0·6	2	8	0·1	127—128	127—128
6-Chloro-4-hydroxycinnoline	0·2	0·6	½	9½	0·2	111—112	111—112
3-Bromo-4-hydroxycinnoline	0·1	0·6	2	8	0·1	144—145	149—150
6-Bromo-4-hydroxycinnoline	0·2	0·6	½	9½	0·2	117—118	126—127
6-Chloro-3-bromo-4-hydroxycinnoline	0·1	0·9	4½	5½	0·1	151—152	153—154
3 : 6-Dibromo-5-hydroxycinnoline	0·1	0·9	5	5	0·1	154—155	159—160

TABLE VII.

Compound.[a]	M. p.	Temp.	Product. M. p.	Recrystallised, m. p.
4-Chloro-3-bromocinnoline	151—152°	95°	135—137°	137—138°
		135	138—139	143—144
4 : 6-Dichloro-3-bromocinnoline	153—154	95	140—143	144—145
4-Chloro-3 : 6-dibromocinnoline	160—161	95	144—145	146—147

(*a*) Named according to probable major component, as revealed in above work.

TABLE VIII.

Compound.	Wt., g.	Time, mins. 135°.	95°.	Product. Wt., g.	M. p.	Recryst., m. p.
6-Chloro-4-hydroxyquinoline	0·5	10	—	0·43	100—101°	103—104° [b]
6-Bromo-4-hydroxyquinoline	0·2	10	—	0·2	108—109	109—110°
3-Bromo-4-hydroxyquinoline	0·5	10	—	0·49	68—69	— [b]
3 : 6-Dichloro-4-hydroxyquinoline	0·2	3	7	0·20	103—104	108—109°
3-Chloro-6-bromo-4-hydroxyquinoline	0·2	3	7	0·21	127—128	130·5—131°
6-Chloro-3-bromo-4-hydroxyquinoline	0·2	2	8	0·21	121—122	124—124·5°
3 : 6-Dibromo-4-hydroxyquinoline	0·2	4	6	0·2	130—131	130·5—131·5°
3 : 3 : 6-Trichloro-3 : 4-dihydro-4-quinolone (?)	0·1	3	7	0·12	91—93	104—105[f]

(*a*) Riegel *et al.* (*loc. cit.*) give m. p. 105°. (*b*) Riegel *et al.* (*loc. cit.*) give m. p. 67—69°. (*c*) 3 : 4 : 6-*Trichloroquinoline*, m. p. 109·5—110° (Found : C, 46·6; H, 2·0. $C_9H_4NCl_3$ requires C, 46·5; H, 1·7%). (*d*) 3 : 4-*Dichloro-6-bromoquinoline* formed white needles (Found : C, 39·3; H, 1·6. $C_9H_4NCl_2Br$ requires C, 39·1; H, 1·5%). (*e*) 4 : 6-*Dichloro-3-bromoquinoline* gave white needles (Found : C, 39·5; H, 1·55%). (*f*) The product on recrystallisation gave only 13% yields of a specimen which did not depress the m. p. of 3 : 4 : 6-trichlorocinnoline. When pure it gave white needles, m. p. 105—105·5° (Found : C, 47·0; H, 1·9%). (*g*) See following table for analyses.

Action of Mixed Phosphorus Chlorides on Bromo-4-chlorocinnolines.—The 4-chlorocinnolines (1 part), prepared as in the foregoing table, phosphorus pentachloride (2 parts), and phosphorus oxychloride (10 volumes) were heated at 95°, or 135—140° under reflux, and worked up as in previous cases. The results are given in Table VII.

Halogen Exchange Reactions and Related Experiments in the Quinoline Series. Preparation of 4-Chloroquinolines.—The 4-hydroxyquinoline (1 part) and phosphorus oxychloride (3 volumes) were boiled under reflux until a clear solution resulted, and then heated at 95° to make a total heating time of 10 minutes. The products were worked up as described for the cinnoline analogues. The results are given in Table VIII.

Action of Mixed Phosphorus Chlorides on Bromo-4-hydroxyquinolines.—The hydroxy-compound (1 part), phosphorus pentachloride (2 parts), and phosphorus oxychloride (10 volumes) were heated at 95°, or 135—140°, for various times, and worked up as with the cinnoline analogues. The results are recorded in Table IX.

TABLE IX.

Compound.	Wt., g.	Conditions.	Product. Wt., g.	M. p.	Recryst., m. p.
3-Bromo-4-hydroxyquinoline	0·5	95°; 2 hours	0·47	65—66°	67—68°
	0·5	135—140°; 2 hours *	0·51	64—65	68—69
	0·5	135—140°; 8 hours *	0·38	67—68	69—70 [b]
6-Bromo-4-hydroxyquinoline	0·5	95°; 2 hours	0·49	109—110	109—110 [c]
	0·5	135—140°; 2 hours	0·49	106—108	111—112
6-Chloro-3-bromo-4-hydroxyquinoline	0·2	95°; 2 hours	0·19	121—122	122—122·5
	0·2	135—140°; 2 hours *	0·19	119—120	122—123 [d]
	0·2	135—140°; 6 hours *	0·19	120—121	122—123
	0·2	135—140°; 24 hours *	0·16	120—121	123—124
3 : 6-Dibromo-4-hydroxyquinoline ...	0·5	95°; 2 hours *	0·39	131—132	131—132
	0·5	135—140°; 2 hours *	0·41	130—131	130—131
	0·5	135—140°; 8 hours *	0·39	128—129	130—131 *
	0·5	135—140°; 24 hours *	0·10	119—120	131—132

(*a*) Bromine visible in reaction vessel. (*b*) This, when pure, formed spiky white needles, m. p. 69—69·5° (Found: C, 45·2; H, 2·15. C_9H_5NClBr requires C, 44·6; H, 2·1%). (*c*) When pure, this gave large white needles, m. p. 110—110·5° (Found: C, 44·6; H, 2·2%). (*d*) As (*c*), m. p. 122—122·5° (Found: C, 40·6; H, 1·5. $C_9H_4NCl_2Br$ requires C, 39·1; H, 1·5%). (*e*) As (*c*), m. p. 130·5—131° (Found: C, 34·6; H, 1·3. $C_9H_4NClBr_2$ requires C, 33·6; H, 1·25%).

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86. *Cinnolines. Part XXVI. Some 4-Cinnolylhydrazines, Their Preparation and Oxidation. Miscellaneous Quinoline Derivatives.*

By K. SCHOFIELD and T. SWAIN.

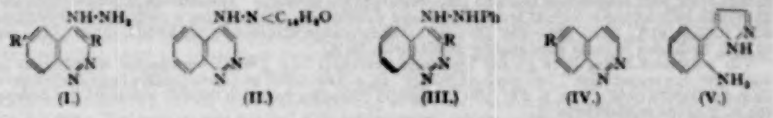
4-Cinnolylhydrazine and its *3-chloro-*, *6-chloro-*, and *6-bromo*-derivatives are described. Except for the 3-chloro-compound, these are oxidised by aqueous copper sulphate to the corresponding *cinnolines*. *4-Phenylhydrazino-* and *3-chloro-4-phenylhydrazino-cinnoline* have been prepared. Attempts to prepare derivatives of 3-aminocinnoline are mentioned, and miscellaneous quinoline derivatives reported.

FROM the reaction between hydrazine and 4-chloroquinaldine Backeberg and Friedmann (*J.*, 1938, 972) obtained either of two products, according to the conditions. Condensation in hot alcohol gave 4-quinaldylhydrazine, whilst reaction at a higher temperature, under pressure, gave an isomeric compound which the authors suggested to be 3 : 4-diaminoquinaldine. Various pieces of evidence made this structure uncertain, but only after this work had begun was it completely disproved (Koenigs and Freund, *Ber.*, 1947, **80**, 143).

Since we desired to prepare 3 : 4-diaminocinnolines, in the light of Backeberg and Friedmann's suggestion it seemed of interest to examine the reaction between 4-chlorocinnolines and hydrazine. Further, 4-cinnolylhydrazines offered the possibility of obtaining, by oxidation, hitherto unknown derivatives of cinnoline unsubstituted at $C_{(4)}$.

4-Chlorocinnoline reacted with hydrazine in alcohol much more slowly and less vigorously than did 4-chloroquinazoline (Dewar, *J.*, 1944, 619; we have repeated the reaction for

comparative purposes). Though only qualitative, the observation is in agreement with the calculations of Longuet-Higgins and Coulson (*J.*, 1949, 971), which indicate that $C_{(4)}$ in quinazoline should be more susceptible to nucleophilic attack than the same position in cinnoline. The product of the reaction was a deep orange-coloured solid, m. p. 293—294° (decomp.), but



after two crystallisations from alcohol its m. p. changed to 226—227° (decomp.). The high-melting form was produced in a reaction carried out under pressure. In view of the behaviour of 4-chloroquinaldine, it was at first thought that isomerisation was involved, but experiment showed that the substances were merely different crystalline forms of *4-cinnolylhydrazine* (I; R = R' = H). Thus, both gave the same *hydrochloride*, and the same *diacetyl* derivative. Any possibility that the low-melting form might be 3 : 4-diaminocinnoline was removed by the formation from it of a *monoformyl* derivative, and of a *product* $C_{23}H_{14}ON_4$ (II) with phenanthraquinone. Finally, both substances gave cinnoline when oxidised with aqueous copper sulphate.

3-Chloro- (I; R = Cl, R' = H), *6-chloro-* (I; R = H, R' = Cl), and *6-bromo-4-cinnolylhydrazine* (I; R = H, R' = Br) were prepared in the same way, but none of these showed polymorphism. Replacement of hydrazine by phenylhydrazine in the reaction gave *4-phenylhydrazino-* (III; R = H), and *3-chloro-4-phenylhydrazinocinnoline* (III; R = Cl).

On oxidation with aqueous copper sulphate 3-chloro-4-cinnolylhydrazine underwent violent decomposition and no recognisable product was isolated. In contrast 6-chloro- and 6-bromo-4-cinnolylhydrazine readily gave *6-chloro-* (IV; R = Cl), and *6-bromocinnoline* (IV; R = Br). Dewar (*loc. cit.*) reported that 4-quinazolylhydrazine was unaffected by acid or neutral copper sulphate, but was oxidised by Fehling's solution, some quinazoline being formed. In our hands, aqueous copper sulphate oxidised 4-quinazolylhydrazine to an unidentified product, the *picrate* of which gave analyses in rough agreement with those required for a hydroxyquinazoline derivative, but which appears to differ from 4-hydroxyquinazoline picrate (Bogert and Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1031).

A few attempts to introduce an amino-group by replacement of halogen in 3-halogenocinnolines failed. 3-Bromo-4-hydroxycinnoline gave no recognisable product when heated with aqueous ammonia in the presence of copper sulphate. 3-Bromo-4-hydroxycinnoline was the only isolable product from the reaction between 4-chloro-3-bromocinnoline and alcoholic ammonia under pressure, but in similar circumstances 3 : 4-dichlorocinnoline gave *3-chloro-4-aminocinnoline*, identical with a specimen prepared from 3-chloro-4-phenoxycinnoline. The use of aqueous ammonia in this case gave a mixture of the 4-amino-compound and 3-chloro-4-hydroxycinnoline. With either aqueous or alcoholic ammonia 4 : 6-dichlorocinnoline gave only 6-chloro-4-hydroxycinnoline. The erratic nature of these results, and the experience of Keneford, Schofield, and Simpson (*J.*, 1948, 358) and of Baker (*J.*, 1948, 1713) with reactions of this type, suggest that they would merit closer examination.

Backeberg and Friedmann (*loc. cit.*), by treating 4-chloroquinoline with hydrazine under pressure, obtained a product, m. p. 129°, which they supposed to be 3 : 4-diaminoquinoline, but which, in view of the work of Koenigs and Freund (*loc. cit.*), must now be regarded as (V). Approaching the problem before the results of Koenigs and Freund appeared, we found it necessary first to compare Backeberg and Friedmann's product directly with authentic specimens of 4-quinolylhydrazine and 3 : 4-diaminoquinoline, which they had not done. 4-Quinolylhydrazine was described by Brydowna (*Rocz. Chem.*, 1932, **12**, 88; only an abstract was available to us), but in trying to repeat the preparation, whilst *4-quinolylhydrazine hydrochloride* was readily obtained, attempts to form the free base gave a white solid, m. p. 135—140° (Brydowna, *loc. cit.*, gives m. p. 140—142°), which rapidly decomposed in air (Knueppel, *Annalen*, 1900, **310**, 82, reported that 6-quinolylhydrazine is likewise unstable). 3 : 4-Diaminoquinoline was obtained by Renshaw, Friedman, and Gajewski (*J. Amer. Chem. Soc.*, 1939, **61**, 3322) by reducing 3-amino-4-phenylazoquinoline, and by the action of ammonia on 3-bromo-4-aminoquinoline. We have now prepared it from 3-nitro-4-aminoquinoline, and characterised it as its *hydrochloride* and *diacetyl* derivative.

Experimental.

(M. p.s are uncorrected.)

4-Cinnolylhydrazine.—(*a*) (i) 4-Chlorocinnoline (2 g.) and hydrazine (2 c.c.; 90%) in alcohol (50 c.c.) were left for 4 days at room temperature. (Under similar conditions 4-chloroquinazoline reacted immediately, with evolution of heat and precipitation of the product.) The mixture of yellow crusts and hydrazine hydrochloride formed was collected and washed with water, giving a deep orange crystalline solid (1·77 g., 91%), m. p. 293—294° (decomp.) (the substance turned deep red at 200—210°). The use of 50% hydrazine hydrate gave slightly lower yields (81%).

(ii) 4-Chlorocinnoline (0·76 g.) and hydrazine hydrate (1·5 c.c.; 90%) were heated for 22 hours at 150—160° in a sealed tube. The product (0·70 g.; m. p. 150—160°) on crystallisation from alcohol gave deep-red leaflets (0·22 g.), m. p. 290—291° (decomp.) (changing colour as before), which did not depress the m. p. of the product from (i).

(*b*) One crystallisation from alcohol of the product from (i) gave bright orange plates, m. p. 296—297°; a second crystallisation from the same solvent gave orange plates, m. p. 224—226° (decomp.) (becoming deep red at 180°). Further crystallisation gave *4-cinnolylhydrazine*, m. p. 226—227° (decomp.) (Found: C, 59·7; H, 5·1; N, 34·7. $C_8H_8N_4$ requires C, 59·9; H, 5·0; N, 34·9%). Either the high- or the low-melting form of the compound dissolved in hot concentrated hydrochloric acid to give very small white crystals of a hydrochloride, m. p. 244—245° (not analysed). Either form when treated with boiling acetic anhydride gave the *diacetyl* derivative, which formed white crystals, m. p. 208—209°, from alcohol (Found: C, 58·6; H, 4·9. $C_{12}H_{12}O_2N_4$ requires C, 58·9; H, 4·9%). Hot anhydrous formic acid likewise gave the *monoformyl* derivative, which formed yellow plates, m. p. 229—230°, from hot water (Found: C, 57·4; H, 4·6. $C_9H_8ON_4$ requires C, 57·4; H, 4·3%). When treated with phenanthraquinone in boiling acetic anhydride, 4-cinnolylhydrazine gave a *monohydrazono*-derivative, which formed glistening red microcrystals, m. p. 267—268°, from alcohol (Found: C, 74·6; H, 4·3; N, 15·0. $C_{22}H_{14}ON_4$ requires C, 75·4; H, 4·0; N, 15·9%).

3-Chloro-4-cinnolylhydrazine.—As in the above case, 3:4-dichlorocinnoline (1·26 g.) and hydrazine (1·5 c.c.; 90%), in alcohol (20 c.c.), gave a product [1·10 g.; m. p. 255° (decomp.)] which formed orange leaflets of *3-chloro-4-cinnolylhydrazine*, m. p. >300° (becoming deep red at 200—220°) (Found: C, 49·4; H, 3·7. $C_8H_7N_4Cl$ requires C, 49·4; H, 3·6%).

6-Chloro-4-cinnolylhydrazine.—In the same way, from 4:6-dichlorocinnoline (1·85 g.), hydrazine hydrate (2 c.c.), and alcohol (120 c.c.), a product was obtained (0·65 g.; m. p. >320°) which formed orange yellow crystals of *6-chloro-4-cinnolylhydrazine*, m. p. >320° (turning deep red at 220°), from alcohol (Found: C, 49·1; H, 3·7%).

6-Bromo-4-cinnolylhydrazine.—4-Chloro-6-bromocinnoline (2·25 g.) likewise gave a product (1·93 g.; m. p. >300°), which was digested with alcohol and reprecipitated from hydrochloric acid solution with ammonia, forming orange microcrystals of *6-bromo-4-cinnolylhydrazine*, m. p. >300° (becoming deep red at 220°) (Found: C, 41·1; H, 3·3. $C_8H_7N_4Br$ requires C, 40·2; H, 2·9%).

Oxidation of 4-Cinnolylhydrazines.—(i) 4-Cinnolylhydrazine (0·2 g.) was heated under reflux with water (2 c.c.), a solution of copper sulphate (4 c.c.; 10%) was added dropwise during 5 minutes (a vigorous reaction ensued), and the mixture was then boiled for ½ hour. Filtration, basification of the filtrate, and ether-extraction removed an oil (0·09 g.). Dissolved in ether (5 c.c.) and treated with picric acid (0·20 g., in benzene (2 c.c.)), this gave a precipitate which formed khaki leaflets, m. p. 191·5—192·5°, from alcohol (Found: C, 47·2; H, 3·7. Calc. for $C_{14}H_9O_7N_7$: C, 46·8; H, 2·5%), identical with cinnoline picrate (Busch and Rast, *Ber.*, 1897, **30**, 521).

(ii) 6-Chloro-4-cinnolylhydrazine (0·5 g.) under the same conditions reacted with moderate vigour and yielded a buff-coloured solid, crystallising from ether–ligroin (b. p. 60—80°) as pale brown lustreless prisms of *6-chlorocinnoline* (0·14 g.), m. p. 119—120° (Found: C, 58·8; H, 3·5. $C_8H_5N_2Cl$ requires C, 58·4; H, 3·1%).

(iii) 6-Bromo-4-cinnolylhydrazine (2 g.) likewise gave *6-bromocinnoline* (0·47 g.), which formed pale buff-coloured needles from ether–ligroin (b. p. 60—80°), m. p. 129—130° (Found: C, 46·9; H, 2·8. $C_8H_5N_2Br$ requires C, 46·0; H, 2·2%).

(iv) Under these conditions 3-chloro-4-cinnolylhydrazine underwent violent oxidation, and the tarry product could neither be crystallised nor converted into a picrate.

Oxidation of 4-Quinazolylhydrazine.—4-Quinazolylhydrazine (0·2 g.), oxidised as above, gave an oily solid which, treated with picric acid (0·1 g.), in alcohol (4 c.c.), gave a *picrate* (0·14 g.), forming yellow microcrystals, m. p. 151—152°, from alcohol (Found: C, 45·4; H, 2·5; N, 16·4. $C_{14}H_9O_7N_7$ requires C, 44·8; H, 2·4; N, 18·6%) (Bogert and Hand, *loc. cit.*, give m. p. 204—205° for 4-hydroxyquinazoline picrate).

4-Phenylhydrazinocinnoline.—A solution of 4-chlorocinnoline (1·9 g.), alcohol (45 c.c.), and phenylhydrazine (3 g.) was left for 3 days at room temperature, filtered from phenylhydrazine hydrochloride, the alcohol removed *in vacuo*, and the tarry residue washed with water and dried on a porous plate. After repeated extraction with ether and crystallisation from alcohol, the solid gave yellow rhombs of *4-phenylhydrazinocinnoline* (0·52 g.), m. p. 238° (decomp.) (Found: 64·1; H, 5·0. $C_{14}H_{12}N_4.1\frac{1}{2}H_2O$ requires C, 63·9; H, 5·5%).

3-Chloro-4-phenylhydrazinocinnoline.—3:4-Dichlorocinnoline (0·5 g.) and phenylhydrazine (0·75 g.), in alcohol (20 c.c.), were left for 6 days at room temperature, and then worked up as above. Crystallisation of the crude product from dilute alcohol gave lustreless brown leaflets (0·39 g.) of *3-chloro-4-phenylhydrazinocinnoline*, m. p. 134—135° (Found: C, 62·5; H, 4·4. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1%).

4-Quinolylhydrazine Hydrochloride.—4-Chloroquinoline (1 g.), hydrazine hydrate (1 c.c.; 90%), and alcohol (10 c.c.) were heated under reflux for 8 hours in an atmosphere of nitrogen. Removal of the alcohol, extraction with ether, concentration of the extract to *ca.* 20 c.c., and drying (Na_2SO_4), followed by passage of dry hydrogen chloride, gave a granular solid. Recrystallisation from dilute alcohol

provided white microcrystals (0·21 g.) of *4-quinolylhydrazine hydrochloride*, m. p. 300—301° (Found: C, 55·1; H, 5·3. $C_9H_9N_3$,HCl requires C, 55·3; H, 5·2%). In other experiments the free base was isolated as a white solid, m. p. 135—140° (Brydowna, *loc. cit.*, gives m. p. 140—142°), which decomposed in a few hours in the air to a black mass with a strong quinoline-like smell.

3 : 4-*Diaminoquinoline*.—(*a*) 3-Nitro-4-aminoquinoline was obtained by a method essentially similar to that since described by Albert *et al.* (*J.*, 1948, 1284), and also from 3-nitro-4-phenoxyquinoline (Schofield and Swain, *J.*, 1949, 1367) as follows. The phenoxy-compound (0·5 g.) was added to ammonium acetate (previously heated at 180°) at 160°, and the temperature raised to 210° during 8 minutes. After 10 minutes at this temperature the mixture was cooled and diluted with water, and the precipitate (0·30 g.) crystallised from alcohol. 3-Nitro-4-aminoquinoline formed yellow needles, m. p. 261—262° (Found: C, 57·2; H, 3·7. Calc. for $C_9H_7O_2N_3$: C, 57·3; H, 3·8%).

(*b*) 3-Nitro-4-aminoquinoline (0·81 g.) in concentrated hydrochloric acid (16 c.c.) was treated with stannous chloride (4 g.) in the same solvent (10 c.c.) at 95°, and the solution heated at this temperature for 2 hours. The mixture was basified with concentrated sodium hydroxide solution, extracted with ether, the extract washed with 6N-sodium hydroxide solution and water, and, after drying (Na_2SO_4), the ether was removed. Crystallisation of the almost pure residue (0·6 g.) from water gave 3 : 4-diaminoquinoline in two forms: one, solvent-free brown prisms, m. p. 171—172° (Found: C, 67·6; H, 5·7. Calc. for $C_9H_9N_3$: C, 67·9; H, 5·7%) (Renshaw *et al.*, *loc. cit.*, give m. p. 174°), and the other, lustreless pale brown needles, m. p. 93—94° (Found: C, 63·6; H, 5·6; N, 24·7. $C_9H_9N_3,\frac{1}{2}H_2O$ requires C, 64·3; H, 5·9; N, 24·9%). The diamine, m. p. 171—172°, when treated in ether with dry hydrogen chloride, gave very small white crystals of a hydrochloride, m. p. 298—299° (not analysed). Boiling acetic anhydride converted the diamine into a *diacetyl* derivative, which crystallised from dilute methanol in small white needles, m. p. 230—231° (Found: C, 62·2; H, 6·3. $C_{13}H_{15}O_2N_3,H_2O$ requires C, 62·3; H, 6·8%).

3-*Chloro*-4-*aminocinnoline*.—(*a*) 3-Chloro-4-phenoxycinnoline (1·5 g.) (see previous paper) was added in one portion to ammonium acetate (9 g.; previously heated to 180°) at 160°. Dilution with water gave a precipitate of 3-chloro-4-hydroxycinnoline (0·19 g.). Basification of the filtrate from this, with ammonia (*d* 0·88), gave a precipitate (0·57 g.) of 3-*chloro*-4-*aminocinnoline*, which formed fine white needles, m. p. 228—229°, from alcohol (Found: C, 53·2; H, 3·4. $C_8H_6N_3Cl$ requires C, 53·5; H, 3·4%).

(*b*) 3 : 4-Dichlorocinnoline (0·5 g.) in saturated alcoholic ammonia (10 c.c.) was heated for 22 hours at 150—160° in a sealed tube. Removal of the alcohol from the product, and crystallisation from dilute alcohol, gave 3-chloro-4-aminocinnoline (0·33 g.), identical with the above.

3 : 4-Dichlorocinnoline (0·5 g.), treated in the same way with aqueous ammonia (5 c.c.; *d* 0·88), gave 3-chloro-4-aminocinnoline (0·08 g.) and 3-chloro-4-hydroxycinnoline (0·23 g.).

Under the above conditions, with either alcoholic or aqueous ammonia, both 4-chloro-3-bromo- and 4 : 6-dichloro-cinnoline gave only the 4-hydroxy-compounds.

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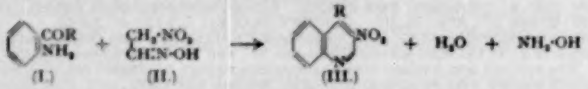
87. *Reactions of Methazonic Acid. Part I. The Preparation of 3-Nitrolepidines and 3-Nitro-4-arylquinolines.*

By K. SCHOFIELD and R. S. THEOBALD.

The course of the reaction between methazonic acid and substituted 2-aminoacetophenones depends on the nature of the substituent. In dilute mineral acid the initial product is a *o*-(2-nitroethylideneamino)acetophenone, or in some cases the oxime of this derivative. *o*-(2-Nitroethylideneamino)acetophenones undergo cyclisation to 3-nitrolepidines and hydrolysis to the parent amines in varying degrees when treated with dilute sodium hydroxide solution. Both they and their oximes are quantitatively cyclised by activated alumina, except in a few special cases. Derivatives of *o*-aminobenzophenone behave similarly, leading finally to 3-nitro-4-arylquinolines. 3-*Nitro*-4-2′-*pyridylquinoline* is described.

3-NITROQUINOLINE and its derivatives have been little studied, probably on account of their inaccessibility. Few synthetic routes to these compounds are known. Only eight cases of direct nitration at the 3-position have been described, and these concern either hydroxy- or amino-quinolines; they are 4-hydroxyquinaldine (Conrad and Limpach, *Ber.*, 1887, **20**, 950; 1888, **21**, 1981; Kermack and Weatherhead, *J.*, 1939, 563), 2 : 4-dihydroxyquinoline (Gabriel, *Ber.*, 1918, **51**, 1500; Ashley, Perkin, and Robinson, *J.*, 1930, 382), *N*-oxides of 4-hydroxyquinaldine and 4-hydroxy-2-phenylquinoline (Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067, 1613), 2-hydroxy-4 : 6-dimethylquinoline (Balaban, *J.*, 1930, 2346), 4 : 6-diaminoquinoline and derivatives (F.P. 779,092; G.P. 613,065; U.S.P. 2,066,730), 7-chloro-4-hydroxyquinoline (Breslow *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1232), and 4-hydroxyquinoline (Schofield and Swain, *J.*, 1949, 1367). Again, apart from the possible preparation of 3-nitrocarbostyril (Friedländer and Lazarus, *Annalen*, 1885, **230**, 243; Decker, *J. pr. Chem.*, 1901, **64**, 101) by a

method of limited utility, only two synthetic routes to 3-nitroquinolines are available. The more recent of these (Uhle and Jacobs, *J. Org. Chem.*, 1945, **10**, 76; Morley and Simpson, *J.*, 1948, 2024) depends on the reaction of an aromatic amine with nitromalonaldehyde, and is limited to 3-nitroquinolines unsubstituted at $C_{(4)}$. The earlier known synthesis utilises the reaction between methazonic acid (II) and an *o*-aminoarylaldehyde or ketone (I; R = H or alkyl), an isatin derivative (I; R = CO_2H), or an anthranilic acid (I; R = OH) (G.P. 335,197, 347,375; Friedländer, **12**, 818; **14**, 521), in dilute mineral acid solution.

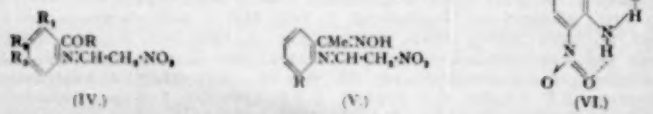


(I.) (II.) (III.)

The methazonic acid synthesis has received little attention, except for the preparation of individual compounds, no systematic study having been reported. Bargellini and Settimj (*Gazzetta*, 1923, **53**, 601) repeated the preparation, described in a patent, of 3-nitroquinoline, Renshaw and Friedman (*J. Amer. Chem. Soc.*, 1939, **61**, 3320; cf. Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 709) reported a yield of 22% in the same instance, and Clemo and Swan raised this to 48% by carrying out the reaction in alcohol containing concentrated hydrochloric acid (*J.*, 1945, 867). Clemo and Swan (*loc. cit.*) also reported successful application of the reaction, though with mediocre yields, to 6-aminopiperonal and 6-aminoveratraldehyde, but Ruggli and Frey (*Helv. Chim. Acta*, 1939, **22**, 1413) obtained only a complex product from 4 : 6-diamino*iso*phthalaldehyde. Several workers have prepared 3-nitro-4-hydroxyquinolines from variously substituted anthranilic acids (Colonna, *Gazzetta*, 1937, **67**, 46; 1939, **69**, 684; Musajo, *ibid.*, 1937, **67**, 222; Bachman *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 365; Breslow *et al.*, *loc. cit.*; Albert, Brown, and Duewell, *J.*, 1948, 1284). It is relevant that these reactions with anthranilic acids always proceed through the intermediate formation of a 2-nitroethylideneamino-compound (IV; R = OH), the cyclisation of which (always in mediocre yield) has only been achieved by sodium acetate in acetic anhydride solution. Applications of the reaction involving isatins will be described in a subsequent paper.

With regard to 2-aminoarylaldehydes and ketones, the original patent describes the use of *o*-aminobenzaldehyde and *o*-aminoacetophenone, and a similar reaction procedure was said to be applicable to various unspecified (including halogeno-)2-aminobenzaldehydes, and to aldehydes and ketones of the naphthalene or anthracene series. Although 2-aminobenzaldehydes are difficult to obtain, many 2-aminoacetophenones are now available, and this fact, coupled with our interest in the possible products and substances to be obtained from them, prompted the present investigation of the scope of the reaction between 2-aminoarylketones and methazonic acid, as a source of 3-nitroquinoline derivatives.

Before examining substituted 2-aminoketones we re-investigated the method described in the patent for preparation of 3-nitrolepidine itself, which consists in treating *o*-aminoacetophenone, in dilute hydrochloric acid solution, with aqueous sodium methazonate, and subsequently acidifying the solution with an unspecified quantity of hydrochloric acid. The yellow precipitate formed at room temperature, said to be a mixture of 3-nitrolepidine and *o*-aminoacetophenone oxime, is stated to be readily freed from the latter by dilute sodium hydroxide solution. We noticed, however, that the initial reaction product dissolved completely in cold dilute alkali, and only after some seconds was the quinoline derivative precipitated. Clearly, 3-nitrolepidine could not have been formed in the original condensation, since it is insoluble in alkali, and it therefore seemed likely that the reaction, like that with anthranilic acids, proceeds in two stages. Recrystallisation of the initial condensation product led to the isolation of o-(*2-nitroethyl-*



(IV.) (V.) (VI.)

ideneamino)acetophenone (IV; R = Me, $R_1 = R_3 = R_4 = H$). Cyclisation of the pure nitroethylideneamino-compound by cold dilute alkali was quantitative, and its facility is in

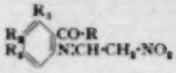
great contrast to the case of the analogous derivatives of anthranilic acids (IV; R = OH), mentioned above. Recovery of 3-nitrolepidine by the method described in the patent never exceeded 14%, based on the amino-ketone. A small improvement (25%) was obtained by careful adjustment of the amount of dilute mineral acid, and by using solid methazonic acid. The obvious discrepancy between the fact that (IV; R = Me, $R_1 = R_2 = R_3 = H$) is quantitatively cyclised to (III; R = Me) by dilute alkali, and the small overall yield of 3-nitrolepidine from the reaction between *o*-aminoacetophenone and methazonic acid under the conditions employed led us to a closer examination of them. This particular reaction has in fact proved to be complex, and further discussion of it is reserved for a later publication.

The more convenient procedure using solid methazonic acid was adopted in all subsequent work with other amino-ketones, and in most cases it also proved necessary to include an organic solvent, usually acetone, in order to ensure homogeneous reaction media. The 4-, 5-, and 6-monosubstituted and 4 : 5-disubstituted 2-aminoacetophenones examined invariably gave compounds of type (IV), always in higher yield than in the case of *o*-aminoacetophenone itself (Table I). Apart from a general tendency for electronegative substituents, particularly *para* to the amino-group, to facilitate the condensation, the results are not entirely clear-cut from the electronic standpoint. One reason for this may lie in the differing solubilities of the products in the varying reaction media, but it may also be that in some cases various side-reactions occur, similar to those shown to a pronounced degree by *o*-aminoacetophenone, though this possibility was not investigated.

Several 3-substituted 2-aminoacetophenones were examined, and in each case the reaction proved in some way unusual. 3-Chloro-, 3-bromo-, and 3-*iodo*-2-*aminoacetophenone* (see below) each reacted with methazonic acid in acetone–dilute hydrochloric acid to give paler products than the normal condensation derivatives (IV). These gave no reaction for a free amino-group, but appeared to be amphoteric since they did not separate from the acid reaction mixture before dilution (in contrast to IV), and also dissolved easily in dilute alkali without cyclising to a quinoline derivative. At present we regard these substances as the oximes (V; R = Cl, Br, or I) of the related 2-nitroethylideneamino-compounds (Table II). After melting with effervescence, they soldified and remelted at a higher temperature. Although the point was not directly proved, it is probable that the second m. p. is that of the corresponding 3-nitrolepidine (see below), formed by elimination of hydroxylamine. Available knowledge of oxime–ketone hydrolysis equilibria (see, *e.g.*, Conant and Bartlett, *J. Amer. Chem. Soc.*, 1932, **54**, 2881) does not make clear why in these cases oxime formation of the acetophenone should be favoured, in contrast to the apparently similar cases of 5-halogeno-2-aminoacetophenones mentioned above. 2-Amino-3-methylacetophenone with an electron-releasing substituent was expected to provide a useful comparison, but in fact it constituted another variation on the normal course of reaction, since 3-*nitro*-4 : 8-*dimethylquinoline* resulted directly in this case. 3-Nitro-2-aminoacetophenone failed to react with methazonic acid in acetone–hydrochloric acid, either at room temperature or at 95°. In view of the relative steric effectiveness of halogen, methyl, and nitro-groups, *e.g.*, in restricting free rotation in the diphenyl series (Gilman, "Organic Chemistry, An advanced Treatise," 1943, p. 362), this failure is probably not due to steric hindrance, and we attribute it to hydrogen bonding in the structure of 3-nitro-2-aminoacetophenone (VI; R = Me).

The second stage of the synthesis of 3-nitrolepidines, the cyclisation of compounds (IV), showed interesting variations. In effecting this step with dilute alkali, besides cyclisation, hydrolysis to the original amine may occur. The ease of these competing reactions varied considerably. Thus 5-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = R_3 = H$, $R_2 = NO_2$) was converted into 3 : 6-*dinitrolepidine* during attempted crystallisation from aqueous acetone, and 4-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = R_3 = H$, $R_2 = NO_2$) was partly cyclised to 3 : 7-*dinitrolepidine* by hot acetone. However, 4-, 5-, and 6-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = NO_2$, $R_2 = R_3 = H$) were all completely hydrolysed to the parent amines by dilute alkali. Although this great ease of alkaline hydrolysis was confined to the *Bz*-nitro-compounds, some degree of hydrolysis did occur with most other compounds of type (IV), as manifested in the diminished yields of 3-nitrolepidines (Table III). The results do not at first sight appear to indicate a consistent effect, depending on the electronic character of the substituent, upon the behaviour of these Schiff's bases towards dilute alkali, but it must be remembered that the two competing reactions of alkaline hydrolysis and cyclisation are each affected in a complicated way by the character of substituents. Depending on its position, a substituent may exert its chief effect on the ketone group, increasing or decreasing its electrophilic nature, upon the azomethine linkage, increasing or decreasing its ease of hydrolysis, or upon the nitroethylideneamino-group, augmenting or

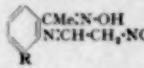
TABLE I.



	R.	R_1	R_2	R_3	Yield, %.[1]	M. p. (decomp.)	Form.	Solvent.[2]	Formula.	Analysis, %. Found. C.	Found. H.	Calc. C.	Calc. H.
(1)	CH_3	H	H	H	27	124—125°	Bright yellow leaflets	b	$C_{10}H_{10}O_3N_2$	58·1	5·2	58·25	4·85
(2)	"	NO_2	H	H	80	187—188	Yellow leaflets	c	$C_{10}H_9O_5N_3$	48·2	3·8	47·8	3·6
(3)	"	H	NO_2	H	85	214—216	Yellow needles	a[3]	"	47·8	3·6	47·8	3·6
(4)	"	H	H	NO_2	55	207—208	Yellow leaflets	Not recryst.[4]	"	46·7	3·6	47·8	3·6
(5)	"	H	Cl	H	75	190—191	Yellow cubes	a	$C_{10}H_9O_3N_2Cl$	49·9	3·7	49·9	3·7
(6)	"	H	H	Cl	50	199—200	Pale yellow solid	c	"	50·0	3·6	49·9	3·7
(7)	"	H	CH_3	H	54	192—193	Yellow prisms	a	$C_{11}H_{12}O_3N_2$	60·0	5·8	60·0	5·5
(8)	"	H	CH_3	CH_3	49	214—215	Pale yellow solid	a	$C_{12}H_{14}O_3N_2$	62·0	6·7	61·5	6·0
(9)	"	H	CH_2O	CH_2O	59	192—193	Orange microneedles	a	$C_{12}H_{12}O_5N_2$	54·3	5·0	54·1	5·3
(10)	"	H	$-[CH_2]_3-$		44	221—222	Yellow needles	a	$C_{12}H_{14}O_3N_2$	63·0	5·7	63·4	5·7
(11)	"	H	$-[CH_2]_4-$		79	212—213	Yellow needles	a	$C_{13}H_{16}O_3N_2$	64·1	6·2	64·6	6·2
(12)	Ph	H	H	H	78	135—136	Yellow needles	b	$C_{16}H_{14}O_3N_2$	68·75	4·3	67·2	4·5
(13)	"	NO_2	H	H	66	163—164	Pale yellow needles	d	$C_{16}H_{11}O_5N_3$	57·6	3·6	57·5	3·5
(14)	"	H	NO_2	H	71	187—188	Yellow needles	a	"	57·9	3·8	57·5	3·5
(15)	"	H	H	NO_2	65	175—176	Yellow microneedles	a	"	57·5	3·75	57·5	3·5
(16)	p-C_6H_4·OMe	H	H	H	79	164—165	Pale yellow needles	b	$C_{14}H_{14}O_4N_2$	64·0	5·0	64·4	4·7

[1] Uncrystallised product—usually substantially pure.
[2] a = Acetone; b = alcohol; c = aqueous acetone; d = acetone–alcohol.
[3] Repeated crystallisation from aqueous acetone caused cyclisation.
[4] Attempted crystallisation from acetone caused cyclisation.

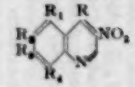
TABLE II.



	R.	Yield, %.[1]	M. p.	Form.	Solvent.	Formula.	Analysis, %. Found. C.	Found. H.	Found. N.	Calc. C.	Calc. H.	Calc. N.
(17)	Cl	46	170° (218—219°)	Pale yellow leaflets	Acetone	$C_{10}H_{10}O_3N_3Cl$	46·5	4·0	16·0	47·0	3·9	16·4
(18)	Br	35	170 (207—208)	Pale yellow cubes	Acetone	$C_{10}H_{10}O_3N_3Br$	39·8	3·5	13·5	40·0	3·4	14·0
(19)	I[2]	38	140 (183—184)	Pale yellow prisms	Acetone	$C_{10}H_{10}O_3N_3I,\frac{1}{2}H_2O$	33·9	2·7	—	33·7	3·1	—

[1] Yield of crude product.
[2] Insufficient of the compound was available for cyclisation.

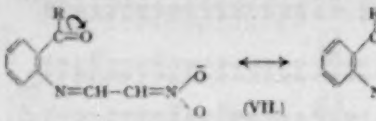
TABLE III.



					Yield, %.[1]						Analysis, %. Found.		Calc.	
R_1.	R_2.	R_3.	R_5.	R_4.	A.	B.	M. p.	Form.	Solvent.[2]	Formula.	C.	H.	C.	H.
CH_3	H	H	H	H	92	Q	117—118°	Colourless needles	a	$C_{10}H_8O_2N$	63·3	3·8	63·8	4·25
"	NO_2	H	H	H	0	75	131—132	Pale pink needles	b	$C_{10}H_7O_4N_2$	50·9	3·2	51·5	3·0
"	H	NO_2	H	H	0	Q	168—169	Pale pink needles	c	$C_{10}H_7O_4N_2$	51·0	3·25	51·5	3·0
"	H	H	NO_2	H	0	Q	182—183	Pale yellow needles	c	$C_{10}H_7O_4N_2$	51·95	3·0	51·5	3·0
"	H	Cl	H	H	86	Q	149—150	Fawn needles	a	$C_{10}H_7O_2N_2Cl$	53·6	3·3	53·9	3·15
"	H	H	Cl	H	60	Q	137—138	Colourless needles	a b	$C_{10}H_7O_2N_2Cl$	54·1	3·5	53·9	3·15
"	H	H	H	Cl	—[3]	Q	218—219	Colourless needles	b	$C_{10}H_7O_2N_2Cl$	54·55	3·4	53·9	3·15
"	H	H	H	Br	—[3]	Q	200—201	Fawn needles	b	$C_{10}H_7O_2N_2Br$	45·3	2·3	44·95	2·6
"	H	CH_3	H	H	44	Q	128—129	Colourless microneedles	b	$C_{11}H_{10}O_2N_2$	65·3	5·0	65·3	5·0
"	H	H	H	CH_3[3]	—	—	116—117	Colourless microneedles	b	$C_{11}H_{10}O_2N_2$	65·25	4·9	65·3	5·0
"	H	CH_3	CH_3	H	55	Q	152—153	Cream microneedles	b	$C_{12}H_{12}O_2N_2$	67·6	6·0	66·65	5·6
"	H	CH_2O	CH_2O	H	32	Q	207—208	Cream microneedles	b	$C_{12}H_{10}O_4N_2$	58·2	5·3	58·1	4·0
"	H	$-(CH_2)_3-$		H	76	Q	115—116	Colourless needles	a	$C_{12}H_{12}O_2N_2$	68·45	5·3	68·4	5·3
"	H	$-(CH_2)_4-$		H	96	Q	135—136	Cream leaflets	a	$C_{13}H_{14}O_2N_2$	69·2	5·85	69·4	5·8
"	H	H	Ac	H[3]	—	—	150—151	Colourless needles	a	$C_{12}H_{10}O_3N_2$	63·0	4·5	62·6	4·35
Ph	H	H	H	H	64	Q	109—110	Colourless needles	a	$C_{11}H_{10}O_2N_2$	71·4	4·1	72·0	4·0
"	NO_2	H	H	H	0	Q	175—176	Colourless needles	a	$C_{12}H_9O_4N_3$	61·5	2·7	61·0	3·1
"	H	NO_2	H	H	0	Q	174—175	Buff needles	a d	$C_{12}H_9O_4N_3$	61·1	3·15	61·0	3·1
"	H	H	NO_2	H	0	Q	171—172	Pale yellow flakes	d	$C_{12}H_9O_4N_3$	60·8	3·0	61·0	3·1
p-C_6H_4·OMe	H	H	H	H	51	Q	128—129	Pale yellow plates	a	$C_{12}H_{12}O_3N_2$	68·0	4·4	68·6	4·3
2-C_5H_4N	H	H	H	H[3]	—	—	113—114	Pale yellow flakes	b	$C_{14}H_{11}O_2N_3$	67·0	4·0	66·9	3·6
											N, 17·3		N, 16·7	

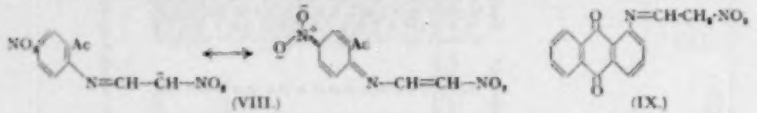
[1] A, dilute NaOH; B, activated alumina; Q, quantitative.
[2] a = Alcohol; b = aqueous alcohol; c = aqueous acetone; d = alcohol–acetone.
[3] See description on p. 403.

detracting from its strength as a pseudo-acid. The importance of the last effect is seen when it is remembered that this mode of cyclisation may involve the anion (VII) of the *aci*-form of (IV). Thus the 5-nitro-group will to a small extent increase the electrophilic nature



(VII.)

of the carbonyl group, and will greatly strengthen the pseudo-acid by increasing the stability of the anion through resonance (VIII), thus facilitating cyclisation. The 4-nitro-group, whilst having a smaller effect on the strength of the pseudo-acid [cf. the dissociation constants (10^5 *K*) of benzoic acid (6·27), *p*-nitrobenzoic acid (37·6), and *m*-nitrobenzoic acid (32·1); Watson,



(VIII.) (IX.)

" Modern Theories of Organic Chemistry," 1941, p. 27], will, on the other hand, exert its main influence by increasing the electrophilic character of the ketone group. In either case, under the faintly alkaline conditions represented by aqueous-acetone solution, cyclisation could be encouraged without serious interference from hydrolysis. With compounds of type (IV), however, electronegative substituents clearly facilitate hydrolysis, so much so that with the *Bz*-nitro-compounds the reaction is so rapid in cold alkali as to forestall cyclisation. In other cases, *e.g.*, that of 2-(2-*nitroethylideneamino*)-5-*methylacetophenone* (IV; R = Me, $R_1 = R_3 = H$, $R_2 = Me$), whilst hydrolysis would be slower, the strength of the pseudo-acid will be decreased, as will the electrophilic activity of the ketone group, so that the yield of 3-*nitro*-4 : 6-*dimethylquinoline* actually realised represents only the unpredictable balance of these complicated factors.

Clearly, the most satisfactory type of cyclising agent for use with compounds (IV) would be one which allowed the conversion of the side chain into the ionised *aci*-form, or alternatively was able to cyclise (IV) without ionisation, and in either case did not allow hydroxylic attack at the azomethine linkage. During experiments on the reaction between methazonic acid and *o*-aminoacetophenone it was noticed that quantitative ring-closure of (IV; R = Me, $R_1 = R_2 = R_3 = H$) to 3-nitrolepidine occurred in aqueous acetone in the presence of activated alumina. This procedure proved applicable, with equal success, in the case of substituted *o*-(2-nitroethylideneamino)acetophenones. Recovery of the substantially pure quinoline derivatives approached the theoretical, even in the cases of (IV; R = Me, $R_1 = H$, $R_2 = H$ or NO_2, $R_3 = NO_2$ or H). The only instance among acetophenone derivatives in which a concomitant degree of hydrolysis occurred under this treatment was that of 6-nitro-2-(2-nitroethylideneamino)acetophenone (IV; R = Me, $R_1 = NO_2$, $R_2 = R_3 = H$), the yield of 3 : 5-*dinitrolepidine* being 75%. This we attribute to steric hindrance between the nitro- and the acetyl group (see below).

The compounds (V), arising from 3-halogeno-2-aminoacetophenones, were also capable of cyclisation to 8-*halogeno*-3-*nitrolepidines* by treatment with alumina. As indicated above, the m. p. of the quinoline corresponded in each case to the second m. p. of the related compound (V).

The ambiguous wording of the original specification (G.P. 335,197) led Hollins (" The Synthesis of Nitrogen Ring Compounds," London, 1924, p. 285) to state that *o*-aminobenzophenone had been utilised in a quinoline synthesis with methazonic acid, but in fact this reaction was not mentioned, and 3-nitro-4-arylquinolines have not been described. Since compounds of the latter type promised to be interesting in several connections, we describe here the reaction of some 2-aminobenzophenones with methazonic acid, reserving for a later paper a description of some reactions of the products obtained.

o-Aminobenzophenone reacted with methazonic acid in acetone–hydrochloric acid to give a high yield of *o*-(2-*nitroethylideneamino*)*benzophenone*. 2-(2-*Nitroethylideneamino*)-4'-*methoxybenzophenone* was obtained similarly. The nitro-2-aminobenzophenones presented a further interesting parallel to the nitro-2-aminoacetophenones. Thus 3-nitro-2-aminobenzophenone failed to react with methazonic acid, presumably because of hydrogen bonding (VI; R = Ph).

The other isomers provided good yields (Table I) of 4-, 5-, and 6-*nitro*-2-(2-*nitroethylideneamino*)-*benzophenone*, which, as expected, proved to be much less labile than their acetophenone counterparts, surviving crystallisation without becoming cyclised.

(IV; R = Ph, R_1 = R_2 = R_3 = H) and (IV; R = *p*-C_6H_4·OMe, R_1 = R_2 = R_3 = H), on dissolution in dilute alkali, were quickly converted into 3-*nitro*-4-*phenyl*- and 3-*nitro*-4-*p*-*methoxyphenyl-quinoline*, respectively, some hydrolysis also occurring. On the other hand, the nitro-compounds were again completely hydrolysed in these circumstances. Once again, activated alumina proved a valuable cyclisation reagent, and by its aid 4- and 5-nitro-2-(2-nitroethylideneamino)benzophenone, as well as the derivatives of *o*-aminobenzophenone and 2-amino-4'-methoxybenzophenone, were cyclised quantitatively. The poor yield of 3 : 5-*dinitro*-4-*phenylquinoline* arising by alumina cyclisation we again attribute to the steric effect of the nitro-group.

It is interesting that 2-2'-aminobenzoylpyridine reacted with methazonic acid in dilute hydrochloric acid to give 3-*nitro*-4-2'-*pyridylquinoline* directly, presumably because of the increased electrophilic activity of the carbonyl group caused by protonisation of the pyridyl nitrogen atom in acid solution. In contrast 1-aminoanthraquinone provided 1-(2-*nitroethylideneamino*)*anthraquinone* (IX), but no method of cyclising this compound has yet been found; both caustic alkali and alumina effected complete hydrolysis, whilst sodium acetate–acetic anhydride left it unchanged.

Various reactions, absorption spectra, etc., of the products described above will be described in the future, as will be the reaction of methazonic acid with some aniline derivatives.

3-*Iodo*-2-*aminoacetophenone*, used in the present work, was obtained by reducing 3-*iodo*-2-*nitroacetophenone*, prepared by a Sandmeyer reaction on 2-nitro-3-aminoacetophenone. It was characterised by conversion into 8-*iodo*-4-*hydroxycinnoline* on diazotisation.

Experimental.

(M. p.s are uncorrected.)

Materials.—The ketones were obtained by known methods as follows: *o*-Aminoacetophenone, 3-, 4-, 5-, and 6-nitro-2-aminoacetophenone, 5-chloro-, 3-chloro-, and 3-bromo-2-aminoacetophenone (Simpson *et al.*, *J.*, 1945, 646; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405; Schofield and Theobald, *J.*, 1949, 796). 2-Nitro-3-aminoacetophenone (Leonard and Boyd, *loc. cit.*; cf. Schofield and Swain, *J.*, 1949, 1367). 4-Chloro-2-aminoacetophenone (Atkinson and Simpson, *J.*, 1947, 232). 2-Amino-3-methylacetophenone (Simpson, unpublished). 2-Amino-5-methyl-, 2-amino-4 : 5-dimethyl-, 2-amino-4 : 5-*cyclo*penteno-, and 2-amino-4 : 5-*cyclo*hexeno-acetophenone (Schofield, Swain, and Theobald, *J.*, 1949, 2399). 2-Amino-1 : 4-diacetylbenzene (Schofield and Theobald, *ibid.*, p. 2404). 6-Aminoacetoveratrone (Simpson, *J.*, 1946, 94). *o*-Aminobenzophenone (Hewett *et al.*, *J.*, 1948, 292). 2-Amino-4'-methoxybenzophenone (Simpson *et al.*, *loc. cit.*). 2-, 3-, 4-, 5-, and 6-Nitro-2-aminobenzophenone (Schofield and Theobald, unpublished). 2-2'-Aminobenzoylpyridine (Schofield, *J.*, 1949, 2408).

Methazonic acid was prepared as described by Steinkopf (*Ber.*, 1909, **42**, 2031), and the product freed from sodium chloride by extraction with ether.

2-(2-*Nitroethylideneamino*)*aryl Ketones.*—In each case the amino-ketone and methazonic acid were dissolved in water, concentrated hydrochloric acid, and, in some cases, acetone, the solution left overnight, and the product collected and crystallised. The following table, in conjunction with Table I, summarises

Compound.	Wt. of ketone (g.).	Vol. of acetone (c.c.).	Vol. of water (c.c.).	Vol. of conc. HCl (c.c.).	Wt. of crude product (g.).	M. p. of crude product (decomp.).
1	5·0	—	200	15	2·34	109—120°
2	0·2	5	5	1	0·22	180—182
3	2·0	150	25	25	2·17 *	204—206
4	0·5	10	5	5	0·38	207—208
5	1·0	25	25	10	0·9	187—188
6	0·5	10	5	5	0·35	194—196
7	0·2	—	5	1	0·16	188—191
8	0·2	5	5	2	0·14	196—201
9	0·2	—	5	1	0·16	175—180
10	1·0	100	—	20	0·61	216—218
11	1·0	150	5	5	1·09	212—213
12	1·0	20	10	10	1·05	130—133
13	1·0	20	5	10	0·85 *	156—158
14	1·0	30	5	10	0·92	168—170
15	0·5	50	5	5	0·42	175—176
16	1·0	50	50	15	1·04	162—163

* Slight concentration of the solution was effected in isolating the product.

the essential data. Weights of methazonic acid are omitted since in all cases 1 equiv. of this compound, with respect to the amino-ketone, was used. The products are, in general, yellow, highly crystalline

substances. Acetone is usually the best solvent for crystallisation, the compounds being but moderately soluble in alcohol, benzene, or chloroform, and almost insoluble in ether or water.

2-(2-Nitroethylideneamino)acetophenone Oximes.—In these cases the 3-halogeno-2-aminoacetophenones were dissolved in acetone, water, and hydrochloric acid, again with 1 equiv. of methazonic acid, and left for 24 hours. The product (see following table) only separated after dilution with water, or removal of acetone followed by dilution (see Table II).

Compound.	Wt. of ketone (g.).	Vol. of acetone (c.c.).	Vol. of water (c.c.).	Vol. of conc. HCl (c.c.).	Vol. of water added (c.c.).	Wt. of crude product (g.).	M. p. of crude product (decomp.).
17	0·5	10	5	2	20	0·33	171—176°
18	0·2	5	2	1	10	0·10	176—178
19	0·5	5	1	1	10	0·26	138—140

Quinoline Derivatives.—(*a*) The nitroethylideneamino-compounds were stirred with 2*N*-sodium hydroxide solution, sometimes with gentle warming. In a few cases the substance dissolved, giving a yellow solution which rapidly deposited the quinoline derivative, or more usually deposition began before dissolution was complete. The products were collected and washed with water, whereupon in most cases substantially pure compounds were obtained. For analysis, crystallisation from acetone, aqueous acetone, alcohol, or aqueous alcohol was effected (Table III). Such alkaline treatment of *Bz*-nitro-2-(2-nitroethylideneamino)-compounds led only to recovery of the parent amine. In other cases, partial hydrolysis was indicated by acidification of the reaction liquor, followed by diazotisation and coupling with alkaline β-naphthol. The 3-halogeno-2-(2-nitroethylideneamino)acetophenone oximes dissolved readily in dilute alkali but no precipitate appeared subsequently, and the acidified solution gave no test for a primary amine.

(*b*) An acetone solution of the nitroethylideneamino-compound was treated with 10 parts of activated alumina, and left overnight. Usually the solution lightened in colour during the cyclisation. Filtration from alumina and removal of acetone usually gave the substantially pure product; occasionally slight stickiness was removed by trituration with a little cold ether. In the cases of 6-nitro-2-(2-nitroethylideneamino)acetophenone and the analogous benzophenone, the products, after removal of the acetone, were oily, and the pure quinoline was only isolated with some difficulty, especially in the second case where the parent amine and derived quinoline showed similar solubilities.

3-Nitro-7-acetyl-lepidine.—A solution of 2-amino-1 : 4-diacetylbenzene (1 g.) and methazonic acid (0·59 g.) in water (50 c.c.) and concentrated hydrochloric acid (10 c.c.) was left for 24 hours, and the precipitate collected, washed, and stirred with dilute alkali. Crude 3-nitro-7-acetyl-lepidine (0·50 g.) separated, and crystallised from alcohol in colourless needles, m. p. 150—151°.

3-Nitro-4-2′-pyridylquinoline.—A solution of 2-2′-aminobenzoylpyridine (1 g.) and methazonic acid (0·55 g.) in water (10 c.c.) and concentrated hydrochloric acid (5 c.c.) was left overnight, neutralised with sodium acetate, and extracted with chloroform. The dried (Na_2SO_4) extract yielded a sticky solid, crystallising in pale yellow flakes of 3-nitro-4-2′-pyridylquinoline (0·87 g.), m. p. 113—114°.

3-Nitro-4 : 8-dimethylquinoline.—A solution of 2-amino-3-methylacetophenone (0·1 g.) and methazonic acid (0·07 g.), in acetone (5 c.c.), water (5 c.c.), and concentrated hydrochloric acid (2 c.c.), was left for 24 hours. Removal of the acetone and addition of water precipitated the crude product (0·09 g., m. p. 103—105°), which separated from dilute ethanol in colourless microneedles, m. p. 116—117°.

3-Iodo-2-nitroacetophenone.—2-Nitro-3-aminoacetophenone (3 g.) in hydrochloric acid (30 c.c. of *ca.* 10*N*.) was diazotised at 0° with aqueous sodium nitrite (20%). Excess of nitrous acid was destroyed with urea, potassium iodide (3·4 g. in 10 c.c. of water) added, and the product collected after 1 hour. Trituration with a little ether, and crystallisation from benzene–ligroin (b. p. 60—80°), gave the substantially pure product (2·2 g.). *3-Iodo-2-nitroacetophenone* formed buff leaflets, m. p. 97—98° (Found: C, 33·77; H, 2·46. $C_8H_6O_3NI$ requires C, 33·01; H, 2·08%).

3-Iodo-2-aminoacetophenone.—The above compound (2 g.) in acetic acid (10 c.c.) at 95° was treated with iron powder (1·5 g. added during 1 hour), additions of water (5 × 2 c.c.) being made at 10-minute intervals. After 1 hour more at 95° the mixture, after dilution, yielded to ether the practically pure product (1·51 g.). *3-Iodo-2-aminoacetophenone* formed golden-yellow prisms, m. p. 57—58° (Found: C, 36·41; H, 4·11. C_8H_8ONI requires C, 36·80; H, 3·09%), when crystallised from ether–ligroin (b. p. 40—60°).

8-Iodo-4-hydroxycinnoline.—The hydrochloride suspension formed from the above amine (0·2 g.) and concentrated hydrochloric acid (5 c.c.) was diazotised at 0° with aqueous sodium nitrite (10%), and the solution left at room temperature for 5 days. The mixture was heated for a short time at 95°, and the precipitate collected (0·04 g.). *8-Iodo-4-hydroxycinnoline* formed pale yellow leaflets, m. p. 261—262° (Found: C, 35·74; H, 1·88. $C_8H_5ON_2I$ requires C, 35·30; H, 1·85%), from ethanol.

Our thanks are due to the Council of University College, Exeter, and to Messrs. Imperial Chemical Industries Ltd. for financial aid, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. S. T.).

WASHINGTON SINGER LABORATORIES,
UNIVERSITY COLLEGE OF THE SOUTH WEST, EXETER. [*Received, September 28th,* 1949.]

NOTES.

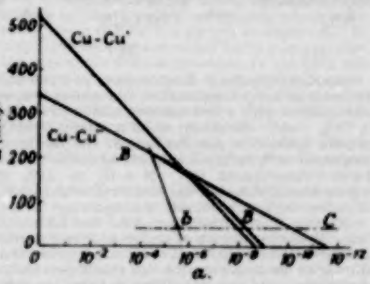
The Behaviour of the Copper Electrode in Dilute Copper Sulphate Solutions. By A. A. Moussa.

The behaviour of the copper electrode in dilute copper sulphate solutions has recently been reported by Tourky and El Wakkad (*J.*, 1948, 749). The potential–activity curves obtained by the authors showed a break which was assumed to signify a pure Cu–$Cu^{\cdot}$ electrode reaction in solutions of cupric-ion activity, $a_{Cu^{\cdot\cdot}}$, lower than $\sim 10^{-4}$. Such an assumption, however, is not justifiable since it would involve a complete breakdown of the equilibrium $Cu^{\cdot\cdot} + Cu \rightleftharpoons 2Cu^{\cdot}$ which should necessarily be maintained whenever metallic copper is in contact with any of its ions in solution. The method to be used to interpret the results and which leads to the above assumption is discussed below, and an explanation for the break observed is put forward.

In the first place, the different values assigned to the equilibrium constant K of the reaction $Cu^{\cdot\cdot} + Cu \rightleftharpoons 2Cu^{\cdot}$ were discussed in detail and 10^{-6} was selected as the most suitable value for calculations. Since, however, a true thermodynamic equilibrium should necessarily satisfy the identity of the different potentials Cu–$Cu^{\cdot\cdot}$, Cu–$Cu^{\cdot}$, and $Cu^{\cdot\cdot}$–$Cu^{\cdot}$ in one and the same solution, the use of any particular value for K other than that which is determined by an equation such as

$$E_{(Cu\text{-}Cu^{\cdot\cdot})} + 0{\cdot}030 \log a_{Cu^{\cdot\cdot}} = E_{(Cu\text{-}Cu^{\cdot})} + 0{\cdot}060 \log a_{Cu^{\cdot}}$$

is not permissible and leads to unnecessary complications. With the values chosen for $E_{(Cu\text{-}Cu^{\cdot\cdot})}$ and $E_{(Cu\text{-}Cu^{\cdot})}$, *viz.* 0·3457 and 0·5220 v., respectively, K amounts to $10^{+4\cdot77}$. Setting K as 10^{-6} instead of $10^{+4\cdot77}$ accounts, although in part only, for the non-identity of the calculated potentials, at least in solutions of high cupric-ion activity where, by subtracting $0{\cdot}5a_{Cu^{\cdot}}$ supposed to be in equilibrium, the original cupric-ion activity remained practically unchanged.



In the second place, the Cu–$Cu^{\cdot\cdot}$ potential in different cupric-ion activities ($a_{Cu^{\cdot\cdot}}$) was calculated as $0{\cdot}5\,(E_{Cu\text{-}Cu^{\cdot}} + E_{Cu^{\cdot}\text{-}Cu^{\cdot\cdot}})$, a procedure which is valid only if the system is in true thermodynamic equilibrium. That this was not the case with the calculated activities would have readily been revealed if solutions of $a_{Cu^{\cdot\cdot}}$ infinitesimally lower than 10^{-6} had been considered, in which case the $Cu^{\cdot\cdot}$–$Cu^{\cdot}$ potential would have been found to acquire, at a limit, an infinite negative potential.

The reason for such an abnormality, as referred to above, lies undoubtedly in setting $a_{Cu^{\cdot}}(s)$ as equal to $\sqrt{[a_{Cu^{\cdot\cdot}}(o) \times K]}$ instead of $\sqrt{[a_{Cu^{\cdot\cdot}}(s) \times K]}$ where $a_{Cu^{\cdot\cdot}}(o)$ is the original cupric-ion activity, and $a_{Cu^{\cdot\cdot}}(s)$ and $a_{Cu^{\cdot}}(s)$ are respectively the cupric- and cuprous-ion activities at equilibrium. With the equilibrium state represented as such $Cu^{\cdot\cdot} + Cu \rightleftharpoons 2Cu^{\cdot}$, the equation $a_{Cu^{\cdot\cdot}}(o) = a_{Cu^{\cdot\cdot}}(s) + 0{\cdot}5\sqrt{[a_{Cu^{\cdot}}(s) \times K]}$ should then hold and can be solved for $a_{Cu^{\cdot\cdot}}(s)$ with any known value for $a_{Cu^{\cdot\cdot}}(o)$ as illustrated by the data in the following table.

$a_{Cu^{\cdot\cdot}}(o)$.	$a_{Cu^{\cdot\cdot}}(s)$.	$a_{Cu^{\cdot}}(s)$.	E.	$a_{Cu^{\cdot\cdot}}(o)$.	$a_{Cu^{\cdot\cdot}}(s)$.	$a_{Cu^{\cdot}}(s)$.	E.
$10^{-0.0000}$	$10^{-4.0000}$	$10^{-4.0000}$	+0·3157	$10^{-4.0014}$	$10^{-4.0000}$	$10^{-4.0020}$	0·1657
$10^{-4.0075}$	10^{-4}	$10^{-4.0041}$	0·2857	$10^{-4.0483}$	10^{-4}	$10^{-4.0242}$	0·1357
$10^{-4.0213}$	10^{-4}	$10^{-4.0084}$	0·2557	$10^{-4.1760}$	10^{-4}	$10^{-4.0321}$	0·1057
$10^{-4.0516}$	10^{-4}	$10^{-4.0260}$	0·2257	$10^{-4.7147}$	10^{-5}	$10^{-4.4260}$	0·0757
$10^{-4.0973}$	10^{-5}	$10^{-5.4264}$	0·1957	$10^{-4.7363}$	10^{-10}	$10^{-5.0262}$	0·0457

N.B.—In obtaining these results the equation was solved by fixing values for $a_{Cu^{\cdot\cdot}}(s)$; the corresponding values for $a_{Cu^{\cdot\cdot}}(o)$ were then calculated. K was set as $10^{-6\cdot77}$.

The above derived activities stand, no doubt, for true thermodynamic equilibria through which the identity of the different potentials is satisfied. Hence, the copper electrode potential, E (column 4), can be readily deduced from any of the following equations:

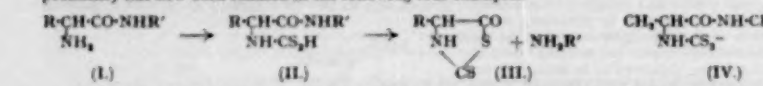
$$E = E_{(Cu\text{-}Cu^{\cdot\cdot})} + 0{\cdot}030 \log a_{Cu^{\cdot\cdot}}(s)$$
$$= E_{(Cu\text{-}Cu^{\cdot})} + 0{\cdot}060 \log a_{Cu^{\cdot}}(s)$$
$$\text{or} = E_{(Cu^{\cdot\cdot}\text{-}Cu^{\cdot})} + 0{\cdot}060 \log a_{Cu^{\cdot\cdot}}(s)/a_{Cu^{\cdot}}(s)$$

Now, by plotting E against $a_{Cu^{\cdot\cdot}}(o)$ the theoretical curve B–B, shown in the figure, is obtained, manifesting a break which possesses its own slope and does not coincide with that for the pure Cu–$Cu^{\cdot}$ system. It should be emphasised, however, that the trend of the curve depends in the first place on the non-appearance of a solid phase that would participate in an ion-determining system, which is hardly the case with aqueous solutions. According to Tourky and El Wakkad's findings (*J.*, 1948, 740), the precipitation pH value of CuOH at a protected copper surface is ~6·8, a value which necessarily approximates to that of the most dilute solution used ($a_{Cu^{\cdot\cdot}} \sim 10^{-6\cdot6}$). As denoted by the theoretical curve B–B, the $a_{Cu^{\cdot}}(s)$ at this dilution is $\sim 10^{-6\cdot9}$. The product $a_{Cu^{\cdot}} \times a_{OH^{-}}$ thus exceeds the solubility product S of CuOH which will then be precipitated with consequent lowering of $a_{Cu^{\cdot}}$ to $S/a_{OH^{-}}$ or $\sim 10^{-9}$ (with 10^{-15} as the most probable value for S). The cuprous-ion activity is thus fixed through the separation of CuOH and will be kept at the above value as long as the pH remains constant. Any excess of cupric ion over that necessary to maintain

the equilibrium state (horizontal line *C*) will be reduced at the metal surface to cuprous, a process which will lead only to the further development of the solid phase separated. The potential, on the E–$a_{Cu^{++}}$ (a) plot, will then be denoted by the point *b*. The trend of the break manifested thereby is not at all comparable with that for the pure Cu–Cu' system; hence its extrapolation to meet the potential axis is insignificant. The author is pleased to know that Prof. Tourky agrees to the above amendment which explains adequately the conclusions in the original paper.—FACULTY OF SCIENCE, FOUAD I UNIVERSITY, ABBASSIA, CAIRO, EGYPT. [*Received, June 16th*, 1949.]

The Removal of Terminal Groups from Peptides. By A. L. LEVY.

COOK, HEILBRON, AND LEVY (*J.*, 1948, 201) described the first example of an unusual reaction of α-amino-amides, namely the cyclisation of *N*-dithiocarboxyglycine amide (II; R = R' = H) with cold mineral acid to give 2-thiothiazolid-5-one (III; R = H) in high yield, with resulting fission of the peptide linkage. An analogous series of transformations has since been carried out with the amides of DL-phenyl-alanine and DL-phenylglycine (Billimoria and Cook, *J.*, 1949, 2323), DL-alanine (Cook and Levy, in the press), and L-tyrosine, L-leucine, DL-methionine, DL-norleucine, L-glutamine, DL-α-amino*iso*butyric acid and DL-aminomalonic acid (Davis and Levy, to be published). A particularly interesting example of this reaction arises when NH_2R' represents an amino-acid or peptide, in which case it should provide a method for the removal, and identification, of the terminal group in the peptide or polypeptide (I). This possibility has now been realised in the following four examples.



DL-Alanylglycine in 2 equivalents of 0·34N-barium hydroxide was shaken with carbon disulphide for 19 hours at room temperature, whereafter evaporation afforded the colourless *barium* salt (IV). This was acidified with N-hydrochloric acid to pH 3—4 to give 2-thio-4-methylthiazolid-5-one (III; R = Me) in 75% yield. Similarly, when DL-alanylglycylglycine was shaken with carbon disulphide and 0·34N-barium hydroxide, acidification of the resulting solution gave (III; R = Me). Glycylglycine was condensed with carbon disulphide as in the two previous examples, whereafter acidification precipitated 2-thio-5-thiazolidone (III; R = H) in 51% yield. DL-Phenylalanylglycine in 2 equivalents of N-potassium hydroxide was combined with carbon disulphide at room temperature, whereafter addition of hydrochloric acid caused the separation of 2-thio-4-benzylthiazolid-5-one (III; R = CH_2Ph).

Finally, it is interesting to note that Léonis (*Compt. rend. Lab. Carlsberg, Sér. Chim.*, 1948, **26**, 315) has utilised the reaction of amino-acids and peptides with carbon disulphide in a quantitative manner to determine the number, and to a limited extent the type, of terminal amino-groups present. In combination with the above results, this should provide a useful method for elucidating the amino-acid sequence in peptides, and this possibility is being investigated.

A preliminary account of another method for the determination of amino-acid sequences, which involves removal of the terminal residue under anhydrous acid conditions as a 3-phenyl-2-thiohydantoin, has been described by Edman (1st. International Congress of Biochemistry, Cambridge, 1949; *Arch. Biochem.*, 1949, **22**, 573).

Experimental.—DL-Alanylglycine (Cook and Levy, in the press) (0·584 g.) in 0·339N-barium hydroxide (23·6 c.c., 2 equivs.) was shaken with carbon disulphide (1 c.c.) for 19 hours in a nitrogen atmosphere, and the resulting orange solution (pH 9) decolorised with a stream of carbon dioxide, which also removed a little free barium hydroxide as barium carbonate. Evaporation in a vacuum yielded *barium* (*N-dithio-carboxyalanyl*)*glycine* (IV), which recrystallised from aqueous ethanol as a colourless, microcrystalline powder, m. p. above 280°, and was dried at 100°/0·1 mm. (Found: C, 19·4; H, 3·7; N, 7·6. $C_4H_5O_3N_2S_2Ba$ requires C, 20·1; H, 2·2; N, 7·8%). The barium salt (1·45 g.) in water (8 c.c.) was acidified with N-hydrochloric acid (8 c.c.) (pH then 3), whereupon 2-thio-4-methylthiazolid-5-one (III; R = Me) crystallised in needles, m. p. 125—126° (0·45 g., 75%). When acidification was effected with acetic acid, (III; R = Me) separated more slowly, and in poorer yield.

DL-Alanylglycylglycine (Fischer, *Ber.*, 1903, **36**, 2982) (0·61 g.) in 0·339N-barium hydroxide (18 c.c., 2 equivs.) was shaken with carbon disulphide (1 c.c.) for 18 hours in a nitrogen atmosphere, and the yellow-orange solution acidified with 2N-hydrochloric acid (3·2 c.c.). Extraction with ethyl acetate, after drying and evaporation, yielded 2-thio-4-methylthiazolid-5-one, m. p. 122—125°.

Glycylglycine (Freudenberg, *Ber.*, 1932, **65**, 1191) (0·66 g.) in 0·339N-barium hydroxide (29·5 c.c., 2 equivs.) was shaken with carbon disulphide (1 c.c.) for 22 hours at room temperature, under nitrogen. The solution went through a maximum orange colour and then became yellower, and a little hydrogen sulphide was produced. A portion (10·5 c.c.) was acidified with concentrated hydrochloric acid (2·5 c.c.), whereupon 2-thiothiazolid-5-one (III; R = H) separated slowly; the solution and crystals were extracted with ethyl acetate to secure the full yield (0·12 g., 51%). The remainder of the dithiocarbamate solution (pH 8) was saturated with carbon dioxide (pH then 6·5), and evaporated to dryness in a vacuum to give yellow barium (*N*-dithiocarboxyglycyl)glycine, which could be precipitated cleanly from aqueous ethanol. It exhibited a bright red fluorescence in ultra-violet light.

DL-Phenylalanylglycine was conveniently synthesised by the procedure of Wessely and Sigmund (*Z. physiol. Chem.*, 1926, **157**, 91) from DL-anhydro-*N*-carboxyphenylalanine and glycine, the former reagent being prepared by an improved method (Levy, *Nature*, in the press). Thus, DL-phenylalanine (4 g.) was suspended in a solution (40% w/w) of carbonyl chloride in toluene (150 c.c.) and gently heated until refluxing. After boiling for a further 4 hours, the clear solution was cooled to 0°, and DL-anhydro-*N*-carboxyphenylalanine (2·7 g.), m. p. 125°, collected. A further 0·5 g. (total yield, 69%), m. p. 124°, was obtained by concentration of the filtrate. In another preparation, phenylalanine (1·0 g.) was heated

under reflux with carbonyl chloride in toluene (10% w/w; 25 c.c.) for 1·25 hours, whereafter the carboxy-anhydride (0·75 g.) crystallised, on cooling, in large blades, m. p. 128—129° to a clear liquid which evolved carbon dioxide vigorously at ~155°. A further 0·06 g. (total yield, 70%), m. p. 127—128°, was obtained from the filtrate.

The peptide (0·3 g.) in 1·1N-potassium hydroxide (2·7 c.c., 2·2 equivs.) was shaken with carbon disulphide (0·5 c.c.) for 3 hours in nitrogen, and the resulting solution extracted with ether, cooled to 0°, and acidified with concentrated hydrochloric acid (10 drops). 2-Thio-4-benzylthiazolid-5-one separated as a gum which slowly solidified, and recrystallised from ethanol in needles, m. p. 159°.

The author is grateful to Sir Ian Heilbron, D.S.O., F.R.S., and Dr. A. H. Cook for their helpful interest in this work, and to the Department of Scientific and Industrial Research for a Senior Research Award.—Imperial College of Science and Technology, S. Kensington, London, S.W.7. [*Received, August 24th*, 1949.]

The Action of Copper on Some Aryldiazonium Sulphates, and the Isolation of Copper Salts.

By Herbert H. Hodgson and John Habershaw.

In view of the recent paper by Cowdrey and Davies (*J.*, 1949, S 48) in which the formation of copper complexes in the Sandmeyer reaction has been reported, some work done by us on a modified Gattermann reaction during 1935—1937 is of interest. It was found that, when copper reacted with aryldiazonium sulphates, deamination occurred to an extent which varied according to the amine employed, and also that the amount of phenol (or naphthol) which could be directly isolated by steam-distillation was generally less than expected. The steam-distillation residues contained copper compounds which were sparingly soluble in boiling water and were decomposed by alkali to give the phenol or naphthol. It would appear, therefore, that the low yield of phenol or naphthol could be accounted for in part by these copper salts. The salts are usually white, or yellow in the case of the nitro-compounds, do not melt but sinter and decompose when heated, and are attacked slowly by cold mineral acids, which become green, while the solid discolours and in some cases becomes black. Unfortunately, only analyses for the copper content of these materials are available but, as can be seen from the table, these correspond to the structure Ar·O·Cu. These and other reaction products are recorded in the table below.

Experimental.—Preparation of the reduced copper. A solution of crystallised copper sulphate (50 g.) in hot water (500 c.c.) was stirred with zinc dust (15 g.), added gradually, and the precipitated copper filtered off and washed.

General reaction procedure. A solution of the amine (5 g.) in sulphuric acid (25 c.c.; *d* 1·84) and water (150 c.c.) was diazotised below 5° with the calculated amount of sodium nitrite in water, the excess of nitrous acid removed by urea, and the mixture treated gradually at room temperature with the copper paste (rather than *vice versa*) to avoid the copper surface becoming coated with reaction products; the mixture was kept overnight, and then steam-distilled to remove the deaminated product (phenol or naphthol) and any volatile diaryl such as diphenyl. The steam-distillate was made alkaline and extracted with ether to remove all but the phenols, and then acidified cold with sulphuric acid and again extracted with ether to remove the latter. The steam-distillation residue was repeatedly extracted with hot water and the extracts were filtered hot; on cooling there separated, after several hours, white or yellow copper compounds of the respective phenol or naphthol. The final residue was extracted with hot aqueous sodium hydroxide to decompose any remaining copper compounds, washed with water, dried, and boiled with benzene to remove non-volatile diaryls and azo-compounds. In the cases of the nitronaphthylamines, the products listed as (1) in the table are those obtained by the addition of copper to the solutions obtained after their diazotisation by the glacial acetic–nitrosylsulphuric acid procedure (Hodgson and Walker, *J.*, 1933, 1620), whereas the products listed as (2) are those obtained after dilution of the acid mixture with ice (100 g.).

Reaction Products (in g.) from Individual Amines (5 g.).

(The amounts are the mean of three experiments.)

Diazonium sulphate.	Deaminated product.	Azo-compound.	Free phenol or naphthol.	Total diaryl or dinaphthyl.	Copper compound. Yield.	Cu, %.	Cu, calc. %.
Benzene	—	0·2	0·5	0·3	None	—	—
o-Chlorobenzene	0·25	1·2	0·1	—	0·25	32·6	33·0
,,	0·6	2·0	0·2	—	0·25	32·6	33·0
o-Nitrobenzene	0·2	—	0·5	2·5	0·25	32·3	31·3
,,	0·4	—	0·6	2·0	0·3	32·7	31·3
,,	0·3	—	0·6	2·5	0·3	32·5	31·3
p-Toluene	0·65	0·48	0·8	—	None	—	—
Naphthalene-1	0·1	—	0·4	—	None	—	—
Naphthalene-2	0·2	—	2·1	—	None	—	—
4-Chloronaphthalene-1	—	2·4	0·5	—	0·5	26·0	26·2
1-Chloronaphthalene-2	—	2·0	0·4	—	0·4	25·8	26·2
2-Nitronaphthalene-1	{0·7 (1) 0·25 (2)	1·0 (1)	0·5	1·3 (2)	0·8	25·8	25·1
4-Nitronaphthalene-1	{0·4 (1) 0·15 (2)	1·5 (1)	0·2	2·0 (2)	0·3	26·0	25·1
1-Nitronaphthalene-2	{0·5 (1) 0·15 (2)	1·5 (1)	0·2	1·3 (2)	0·3	25·9	25·1

In each case, the copper compound was ignited with nitric acid and the copper weighed as oxide after ignition.

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division for gifts of chemicals.—TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, September 22nd,* 1949.]

The Reduction of Toluene-p-sulphonic Esters. By G. W. KENNER and M. A. MURRAY.

THE reduction of toluene-*p*-sulphonic esters has recently been studied by Schmid and Karrer (*Helv. Chim. Acta*, 1949, **32**, 1371) using lithium aluminium hydride and by ourselves (*J.*, 1949, S 178) using Raney nickel and hydrogen; the results of these two investigations form an interesting contrast. Whereas the customary hydrogenation converts the aryl toluenesulphonates into aromatic hydrocarbons, and the alkyl esters into alcohols, lithium aluminium hydride, in general, yields phenols and de-oxygenated aliphatic compounds respectively. As we remarked in our paper, this latter mode of fission is in line with the well-known heterolytic decompositions of toluene-*p*-sulphonic esters by nucleophilic reagents, and Schmid and Karrer (*loc. cit.*) have also drawn attention to the analogy between the reactions of lithium aluminium hydride and those of the Grignard reagents. It is therefore suggested that these reductions may be represented as follows, lithium aluminium hydride being regarded as a source of potential hydride ions:

$$Ar\text{-}O\text{-}SO_2\text{-}C_7H_7 \xrightarrow{H^+} Ar\text{-}H + HO\text{-}SO_2\text{-}C_7H_7$$
$$Ar\text{-}O\text{-}SO_2\text{-}C_7H_7 \xrightarrow{H^-} Ar\text{-}OH + HO\text{-}SO\text{-}C_7H_7, \text{ and reduction products}$$

$$Alk\text{-}O\text{-}SO_2\text{-}C_7H_7 \xrightarrow{H^+} Alk\text{-}OH + \text{reduction products of } HO\text{-}SO\text{-}C_7H_7$$
$$Alk\text{-}O\text{-}SO_2\text{-}C_7H_7 \xrightarrow{H^-} Alk\text{-}H + HO\text{-}SO_2\text{-}C_7H_7$$

The already publicised reactions of lithium aluminium hydride, for example with carbonyl groups (see, *inter alia*, Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197, 2548) and epoxides (see, *inter alia*, Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1885), as well as the characteristic inertness of unpolarised double bonds to this reagent are in accord with this interpretation. Further, at the suggestion of Professor V. Prelog, one of us allowed lithium aluminium hydride to react with strychnine methosulphate and found the major product to be strychnidine. That is, the amide linkage had been reduced and the methyl group, which is more susceptible to S_N2 reactions than the higher alkyl groups (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 607), had been displaced:

$$\rangle N^+ - CH_3 \xrightarrow{H^-} \rangle N + CH_4$$

The exceptional cases of 3-toluene-*p*-sulphonyl 1 : 2-5 : 6-di*iso*propylidene glucose and 1-toluene-*p*-sulphonyl 2 : 3-4 : 5-di*iso*propylidene fructose (Schmid and Karrer, *loc. cit.*) may well be examples of steric hindrance in such reactions.

Strychnidine.—Strychnine methosulphate (Clemo, Perkin, and Robinson, *J.*, 1927, 1589) (4·60 g.) was added during 15 minutes to lithium aluminium hydride (1·14 g.) in tetrahydrofuran (25 c.c.) with cooling. The mixture was shaken for ½ hour without cooling and then heated to boiling during 1½ hours before being poured into ice-water (70 c.c.). Chloroform (50 c.c.) was then added, the solid filtered off, and the filtrate extracted with chloroform after being made alkaline with ammonia. The solid was stirred with 3 portions of chloroform, and the combined extracts of the aqueous and the solid phase were dried and evaporated. Recrystallisation of the resulting solid (2 g.) from ethoxyethanol yielded strychnidine, m. p. 258° (in vac.; corr.) (undepressed by an authentic specimen), $[\alpha]_D^{20}$ −63° ± 3° (*c*, 1·5 in chloroform) (Found, in material sublimed at 150°/0·01 mm.: C, 78·8; H, 7·45. Calc. for $C_{21}H_{24}O_2N_2$: C, 78·7; H, 7·55%). UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE, and ROYAL HOLLOWAY COLLEGE, UNIVERSITY OF LONDON. [*Received, October 14th,* 1949].

The Preparation of 2-Ethoxyethyl Chlorides and Bromides. By D. E. AMES and R. E. BOWMAN.

IN connection with another investigation we wished to prepare certain 2-alkoxyalkyl halides. There are many examples in the literature of such preparations, differing, however, very considerably with respect to the yields obtained. Bennett and his co-workers (*J.*, 1925, **127**, 1279; 1927, 270, 472), L. I. Smith *et al.* (*J. Org. Chem.*, 1939, **4**, 334), and Hurd and Fowler (*J. Amer. Chem. Soc.*, 1939, **61**, 249) used the appropriate thionyl halide in the presence of a base (Darzens, *Compt. rend.*, 1911, **152**, 1314). Use of phosphorus tribromide has been described by Palomaa and Kenetti (*Ber.*, 1931, **64B**, 797), Harrison and Diehl (*Org. Synth.*, **23**, 32), Chalmers (*Canadian J. Res.*, 1932, **7**, 464), and Hurd and Fowler (*loc. cit.*) for the same purpose.

We employed the readily available 2-ethoxyethanol as model substance using Darzens's method with thionyl chloride and bromide under conditions described by Gerrard (*J.*, 1939, 100), and thereby obtained excellent, reproducible yields. Furthermore, we have confirmed the finding that the use of more than one molecular proportion of base reduces the yield although excess of thionyl halide is not deleterious.

The following method gave the best results: a mixture of the dry, purified base (1 mol.) and 2-ethoxyethanol (1 mol.) was cooled to −20° and the appropriate thionyl halide (1·1 mols.) added

with stirring at such a rate that the temperature did not rise above 0°. The reaction mixture was then allowed to warm to room temperature and thereafter heated at 100° (bath) for 2 hours. When cold, it was treated with dilute hydrochloric acid, and the product isolated with ether. The ethereal extracts were washed with dilute sodium hydroxide solution and dried (Na_2SO_4), and the solvent was removed by careful distillation through a Vigreux column. The product was then obtained by distillation of the residue. In this manner 2-ethoxyethyl chloride was obtained (yields in parentheses) by use of dimethylaniline (61%), pyridine (80%), or quinoline (84%). The bromide was obtained in 70% yield with pyridine as base.

With dimethylaniline as base, an increase in the proportion of thionyl chloride (3 mols.) was without significant effect on the yield of product. Excess of base, *viz.*, 2-ethoxyethanol (1 mol.), dimethylaniline (2 mols.), and thionyl chloride (3 mols.), under the same conditions reduced the yield of chloride to 40%.

We are indebted to the Medical Research Council for a grant which has enabled one of us (D. E. A.) to take part in this work.—Birkbeck College, London, E.C.4. [*Received, October 21st*, 1949.]

Diterpenes. Part II. The Optical Rotation of Hosking's Kaurene. By Lindsay H. Briggs and W. I. Taylor.

Hosking (*Rec. Trav. chim.*, 1928, **47**, 578; 1930, **49**, 1036) described a diterpene, kaurene, m. p. 57—58°, from the essential oil of *Agathis australis* ("kauri"), and its hydrochloride, m. p. 110—111°, from which the hydrocarbon was regenerated by the action of alcoholic potassium hydroxide. It has been shown in Part I (*J.*, 1948, 1888) that the diterpene occurring in the oil has a lower m. p. (50°) and that it is isomerised to *iso*kaurene, m. p. 64°, on treatment of its hydrochloride with alkali. Both kaurene and *iso*kaurene form the same hydrochloride and dihydro-derivative, typical of compounds whose isomerism is caused by the change of the double bond from an exocyclic to an endocyclic position. The m. p.s of Hosking's products are intermediate between those of kaurene and *iso*kaurene and it would appear that in both cases he was dealing with an impure form of *iso*kaurene.

A larger discrepancy occurs, however, in the optical rotation of Hosking's and our product. Although Hosking's liquid diterpene fraction from which the kaurene was isolated was optically active, all the rotations observed on solid products derived therefrom had zero values. On the other hand, all our products had definite lævorotations (*loc. cit.*). With the number of asymmetric centres present in any tetracyclic structure possible for kaurene on an isoprene plan (possibly five) it is difficult to see how racemisation of all centres had occurred in Hosking's manipulation.

Through the courtesy of Professor L. Ruzicka, to whom we express our thanks, we have been able to re-examine an original sample of dihydrokaurene obtained by Hosking. No sample of kaurene remained but the dihydro-derivative on crystallisation from acetic acid had m. p. and mixed m. p. 86°, with $[\alpha]_D^{20}$ −32° ± 2° (*c*, 2·0 in chloroform) in agreement with that recorded by Briggs and Cawley in Part I (*loc. cit.*), *viz.*, $[\alpha]_D^{20}$ −35·7° (*c*, 0·33 in chloroform), from which we conclude that the original kaurene was active also.

No adequate explanation can be advanced to explain these contrasting results.

One of us (W. I. T.) is indebted for a National Research Scholarship of New Zealand.—Auckland University College, Auckland, New Zealand; and Eidg. Technischen Hochschule, Zürich. [*Received, November 14th*, 1949.]

Dimorphism in Acenaphthene-3-aldehyde. By John H. Gorvin.

The aldehyde prepared from acenaphthene by the Gattermann synthesis was reported by Hinkel, Ayling, and Beynon (*J.*, 1936, 344) to melt at 87°; subsequently Fieser and Jones (*J. Amer. Chem. Soc.*, 1942, **64**, 1666) obtained by the *N*-methylformanilide—phosphorus oxychloride procedure a substance, m. p. 107·4—108°. Each of these products gave evidence of being acenaphthene-3-aldehyde.

In the present investigation no difficulty was encountered in the preparation of acenaphthene-3-aldehyde, m. p. 107—107·5° (corr.), by either method. It was therefore of interest to examine the product obtained by the earlier workers, and I am very grateful to Dr. L. E. Hinkel and Mr. E. E. Ayling, of University College, Swansea, for making available a specimen of their original crude aldehyde. The principal contaminant of this material proved to be a very small amount of tar which was difficult to remove completely by crystallisation from light petroleum (b. p. 60—80°); the crystals obtained had m. p. 87°. When however the warm petroleum solution was filtered through activated alumina held in a sintered-glass Büchner funnel the clear filtrate deposited crystals, m. p. 107—107·5°, of authentic acenaphthene-3-aldehyde. A similar product was obtained on hydrolysis of the anil, m. p. 97°, prepared by the Swansea workers (*loc. cit.*) from their aldehyde, m. p. 87°.

In preparations of the aldehyde carried out in these Laboratories the light-petroleum mother-liquor on one occasion deposited crystals, m. p. 85°, showing no melting-point depression on being mixed with the material of Hinkel, Ayling, and Beynon (*loc. cit.*). This substance similarly crystallised as the high-m. p. form after filtration of its light-petroleum solution through alumina.

As the amount of tarry material present in the crude aldehyde was quite inadequate to account for a melting-point lowering of 20° it was concluded that the impurity had stabilised a polymorphic modification of the aldehyde and had inhibited the change to the stable, high-m. p. form which would be expected to occur on fusion or long storage. Confirmation of this was obtained by undisturbed cooling of pure molten acenaphthene-3-aldehyde; often the melt crystallised rapidly to give the high m. p. form but sometimes it could be successfully supercooled with eventual solidification to a crystalline mass, m. p. *ca.* 89°, fusion of which was usually followed by crystallisation of the melt in the form, m. p. 107—107·5°,

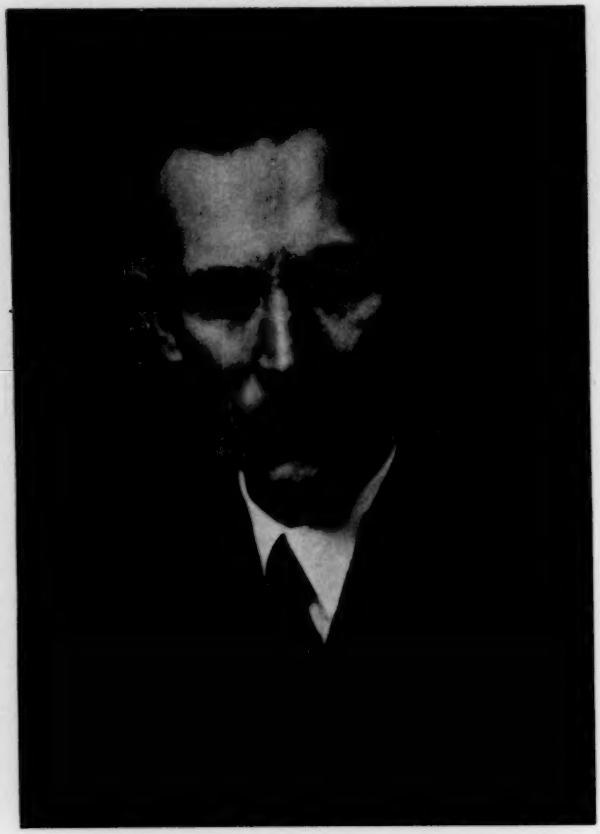
The ease of conversion of the metastable into the stable form of the pure aldehyde is in striking contrast to the persistence of the low-melting form in its contaminated state. A rather similar case has previously been noted (Gorvin, *J.*, 1945, 734) in ethyl 3-sulphanilamidobenzoate; the form, m. p. 105°, recorded by an earlier group of workers persisted until the compound was carefully purified, whereupon conversion into a stable form, m. p. 153°, occurred immediately on fusion at the lower temperature. These examples of metastable states stabilised by impurities emphasise the importance of removal of all traces of contaminating tarry material from organic substances before recording physical constants; the increasing availability of activated adsorbents has in many cases greatly simplified this procedure.—WELLCOME LABORATORIES OF TROPICAL MEDICINE, LONDON, N.W.1. [*Received, November 18th*, 1949.]

Synthetic Ribonucleoside-2′ Phosphates: a Correction. By D. M. BROWN, L. J. HAYNES, and A. R. TODD.

IN a recent paper Michelson and Todd (*J.*, 1949, 2476) described the synthesis of a number of mononucleotides derived from the natural ribonucleosides, adenosine, guanosine, cytidine, and uridine. In the course of this work the benzylidene derivatives of adenosine and guanosine were phosphorylated and the protecting groups subsequently removed, yielding products which were assumed to be adenosine-2′ phosphate and guanosine-2′ phosphate. This assumption appeared to be warranted on the evidence that (i) the condensation product of guanosine with benzaldehyde was shown by Bredereck and Berger (*Ber.*, 1940, **73**, 1124) and by Gulland and Overend (*J.*, 1948, 1380) to be 3′ : 5′-benzylidene guanosine, and (ii) the behaviour of the products on acid hydrolysis was analogous to that of the substances described in the literature as uridine-2′ phosphate (Gulland and Smith, *J.*, 1947, 338) and cytidine-2′ phosphate (Gulland and Smith, *J.*, 1948, 1527), the two latter compounds having been prepared in strictly analogous fashion from benzylidene uridine and benzylidene cytidine.

Further investigation has shown, however, that the product we described as adenosine-2′ phosphate is in fact essentially adenosine-5′ phosphate; the latter compound can be isolated in high yield from the amorphous nucleotide described by Michelson and Todd (*loc. cit.*) and has been identified by periodate titration (absorption of 1 mole of oxidant/mole) and by comparison of chemical and physical properties including *X*-ray diffraction photographs. In the same way it has been found that the alleged cytidine-2′ phosphate of Gulland and Smith (*loc. cit.*), as prepared by us, is in fact cytidine-5′ phosphate. From the method of preparation and particularly from consideration of their acid hydrolysis curves, there can be little doubt but that the products described as uridine-2′ phosphate (Gulland and Smith, *loc. cit.*) and guanosine-2′ phosphate (Michelson and Todd, *loc. cit.*) also consist essentially of the corresponding 5′-phosphates.

The origin of 5′-phosphorylated nucleosides in these synthetic experiments is not yet clear but their production would seem to indicate either that a facile and unsuspected migration of acyl groups occurs at some intermediate stage or that the experimental evidence for the 3′ : 5′-structure of the benzylidene nucleosides (Gulland and Overend, *loc. cit.*) is not valid. If the former explanation should prove correct, the finding might well be of significance in the interpretation of nucleic acid structure based on hydrolytic studies. The whole question is at present being investigated in this laboratory, together with the problem of the synthesis of the true nucleoside-2′ phosphates and our results will be communicated in detail later. It seems, however, desirable at this stage to draw attention to the fact that the synthetic nucleotides described in the literature as nucleoside-2′ phosphates do not have the structure assigned to them, the more so as the recent findings of Carter and Cohn (*Fed. Proc.*, 1949, **8**, 190) have aroused interest in nucleoside-2′ phosphates as possible hydrolysis products of yeast ribonucleic acid.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 5th*, 1949.]



J. N. Brönsted

[To face p. 609.

The Brönsted Memorial Lecture.

Delivered before the Chemical Society in London on February 3rd, 1949.

By R. P. Bell, M.A., F.R.S.

It is a difficult task to commemorate and appraise a great man like Brönsted, especially for one thirty years his junior in age, and so much his junior in science. This difficulty is increased by a difference in nationality, and I feel therefore that I ought to begin by acknowledging my debt to the many friends in Denmark who have helped me in the preparation of this lecture. I must mention especially Mrs. Brönsted, who has provided me with much material, especially about Brönsted's early life, and Professor Christiansen, who has made available to me the manuscript of his own memorial lecture to Brönsted. What I have to say owes a very great deal to their willing co-operation.

I shall begin by giving an outline of Brönsted's life and career, followed by some account of his scientific work, and finally I shall try to give a general picture of him as a scientist and as a man.

Johannes Nicolaus Brönsted was born on February 22nd, 1879, in Varde, a small town in West Jutland. His father was a civil engineer employed by "Hedeselskabet," a corporation founded to reclaim moorland by draining, irrigation, and planting. His mother died shortly after his birth, but his father remarried shortly afterwards, and the family moved to a farm in the heart of Jutland, where the young Brönsted and his elder sister spent most of their childhood. This period laid the foundation for the love of country things and country people which played such a great part in his later life. When he was twelve years old his family moved to Aarhus, the second largest city in Denmark, but still an essentially rural environment. He went to school there and seems to have been an apt pupil, particularly in mathematics. There was, of course, no school instruction in chemistry at that time, but Brönsted's interest in the subject was a very early one, his first source of information being an agricultural dictionary which he found in the attic. He did primitive experiments at home in the usual fashion, and the spirit lamp and balance which he used are still in existence.

His father died, in 1893, leaving the family in straitened circumstances. Several friends of the family felt that the young Brönsted ought to begin to earn his living, but his mother recognised his promise and was determined to give him and his sister a good education even if it meant considerable sacrifices. The family moved to Copenhagen, and Brönsted attended the Metropolitan School there, where he found not only a high educational standard, but also a remarkably stimulating set of school-fellows. Of the twenty boys in his class, two became bishops, two distinguished physicians, and five professors. One of the latter was Niels Bjerrum, his closest friend for many years, and his chief rival in making Danish physical chemistry world-famous. Brönsted matriculated in 1897, and went to study at the Polytechnic Institute in Copenhagen, where he met Charlotte Louise Warberg, whom he married in 1903. His studies seem to have sat lightly on his shoulders, and he found plenty of leisure to cultivate other interests such as philosophy, art, poetry, and music. It was at first intended that he should become an engineer like his father, but after taking his first degree in that subject in 1899 he changed over to pure science, and took his "Magister" degree in chemistry in 1902. At that date this degree was something of a rarity, especially in chemistry, and Brönsted's friends used "Magister" as a nickname for many years afterwards.

There was no academic position immediately available, and Brönsted worked for a short time in an electro-technical concern. However, he soon returned to the University Chemical Laboratory, and was made an assistant there in 1905. He worked there on his affinity measurements, and in May 1908 presented the third paper in this series (on mixtures of sulphuric acid and water) for his doctorate degree. In the same year a new chair of chemistry was instituted in Copenhagen which combined the duties of teaching physical chemistry to the University students, and inorganic chemistry to students at the Polytechnic Institute. The two competitors for this chair were Brönsted and Niels Bjerrum, who had been Brönsted's class-mate at school, and had taken his doctorate degree in the same year. It must have been a very difficult decision for the judges to make, but their choice finally fell on Brönsted, who was appointed at the early age of 29. The news reached the Brönsted family in a dramatic way: one day just before Christmas a goods train stopped at the bottom of their garden in the country, and a railway official descended bearing a telegram of congratulation from Bjerrum.

This appointment fixed the whole of Brönsted's subsequent career, as he held the chair until

his death 39 years later. His laboratory was at first in the Polytechnic Institute, and for a time facilities were very limited, as physical chemistry was a new subject and the laboratory had to be equipped from scratch. However, conditions gradually improved, and in 1919 he was relieved from the onerous task of teaching elementary inorganic chemistry. The greatest change in his working conditions resulted from his visit to the United States in 1926—27, when he was able to discuss the possibility of financing a new physicochemical laboratory in Copenhagen. The International Education Board finally met the cost of a new University Physicochemical Institute, which was completed in 1930. Here Brönsted had not only ideal working conditions, but also a delightful official residence where he and his family could exercise their hospitality and charm.

I shall now give some account of Brönsted's contributions to physical chemistry, not in strictly chronological order, but under their main headings.

The most important general interest in Brönsted's scientific work was undoubtedly thermodynamics. His earlier work dealt entirely with this topic, and even his later work on reaction kinetics has a strong thermodynamic flavour. His series of thirteen experimental papers on "Affinity" appeared during the years 1906—18, and constitute a veritable text-book of thermodynamics. Although Brönsted is well known for his later work on the thermodynamics of dilute electrolyte solutions, it is probably not generally realised how much he contributed to the fundamentals of chemical thermodynamics, where he can be ranked with Nernst and G. N. Lewis. At that time, although it was generally accepted that the affinity of a chemical process was measured by the maximum work and not by the heat of reaction, there were very few accurate or systematic measurements of affinity, and it was this gap which Brönsted set out to fill. In 1906 he showed how the heat and free energy changes in the interconversion of rhombic and monoclinic sulphur could be measured over a range of temperature, and he also speculated as to how affinity changes could be calculated from purely thermal quantities. It was of course Nernst, and not Brönsted, who first solved this last problem successfully, but Nernst himself acknowledged the importance of Brönsted's work in pointing the way. In a later paper in the same series (1910) Brönsted dealt with the thermodynamics of water–sulphuric acid mixtures, and gave one of the first correct treatments of the relations between the various differential and integral thermodynamic quantities in a mixture. In this paper he showed great ingenuity in combining vapour pressure, E.M.F., and calorimetric measurements, and (as in all these early papers) in obtaining accurate results with very modest resources.

Brönsted was always skilled at devising applications of E.M.F. measurements, and one example of this was his measurement of the free energy of formation of naphthalene picrate from its solid constituents, not at first sight a promising system for study by E.M.F. methods. Brönsted pointed out in 1911 that the free energy of this change was measured by the E.M.F. of the cell:

$$\text{Picrate electrode}|\text{solution I}|H_2Pt,\ PtH_2|\text{solution II}|\text{Picrate electrode}$$

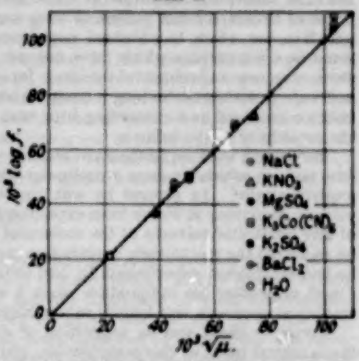
where solution I is saturated with picric acid, and solution II with naphthalene + naphthalene picrate. Brönsted suggested using mercury–mercurous picrate for the picrate electrode, but was unable to make measurements on the above cell because the picrate solutions were reduced at the hydrogen electrodes. He was therefore compelled to use a very ingenious but laborious indirect method of measurement. It is interesting to note that in Oxford we have recently been able to measure the E.M.F. of the cell originally proposed by Brönsted by replacing the hydrogen electrodes by glass ones (which of course were not available to him): the value obtained for the free energy of formation is exactly the same as that obtained in 1911 by the indirect method (Bell and Fendley, *Trans. Faraday Soc.*, 1949, **45**, 121).

Brönsted's thermodynamic studies soon led him into the field of electrolytes, first through E.M.F. measurements, and later through studies of solubility. It was becoming clear, partly through the work of Bjerrum, that very many electrolytes were completely dissociated in solution, and that their deviations from ideal thermodynamic behaviour could not be explained in terms of any association equilibrium. The concept of "activity" had been introduced by G. N. Lewis, and various authors had suggested that electrostatic forces between the ions might be of importance. Brönsted's approach was essentially an experimental one, and his solubility measurements became famous in 1924, when with LaMer he published data on activity coefficients of ions in very dilute salt solutions which provided a most striking confirmation of the theoretical treatment of Debye and Hückel, published while the work was in progress. It should, however, be stressed that this publication with LaMer was really the fifth

of a series of papers on solubility, starting in 1919, interspersed with a number of other papers on the properties of ionic solutions. It is in fact remarkable how many important laws Brönsted was able to discover on the basis of his carefully designed and accurate experiments, in most cases before any theoretical basis for these laws was available. Thus he was able to show that the deviations of ionic solutions from ideal behaviour increase greatly with an increase in the charges on the ions present, and that in a solution containing several electrolytes the thermodynamic behaviour of a given ion is mainly a function of the ionic strength μ, defined as $\mu = \frac{1}{2}\Sigma m_i z_i^2$, where m_i is the concentration of an ion of charge z_i, and the summation extends over all the ions in the solution. In more concentrated solutions ions show individual properties not depending only on their charge, and Brönsted's "Principle of the specific interaction of ions" (1921) states that the individual properties of a given ion depend mainly on the ions of opposite charge which are present in solution. Brönsted's investigations on the effect of salts on ionic equilibria will be described under his kinetic work, but one simple principle is worth mentioning here: that even an ionic equilibrium will obey the classical law of mass action in presence of a large excess of non-participating salt. All these principles were later shown to have theoretical bases, and if we add to Brönsted's work the equally important investigations of his countryman Bejerrum, it will be seen that Denmark has had an altogether disproportionate share in the experimental foundations of the modern theory of electrolytes.

Most of Brönsted's solubility determinations, and many of his other researches, were carried out with the cobaltammines. These had been studied in great detail from the preparative point of view by S. M. Jörgensen, Brönsted's teacher, and he therefore had to hand large numbers of specimens and much information about these compounds. This was naturally a piece of good fortune, but Brönsted's genius lay in realising how admirably suited they were for his purposes. By suitable variations in the nature of the six groups co-ordinated to the central atom, ions can be produced with valencies varying from $+3$ to -3, and by combining these ions with one another or with other anions or cations it is possible to obtain salts of many charge-types and of widely varing solubility. Most of these salts are well-defined and crystalline, and they can be determined accurately even in very dilute solution by the simple process of treatment with sodium hydroxide and distillation of the ammonia into standard acid. These properties made them almost ideal for investigation of solubilities in salt solutions, but there was a great deal of ground-work to be done before the most suitable salts could be chosen: thus in his 1920 paper he measured the solubilities of 90 salts at two temperatures. The salts finally used by Brönsted and LaMer were the following:

Fig. 1.



The relation between the activity coefficient f and the ionic strength μ for a uni-bivalent cobaltammine salt in the presence of solvent salts of various types. The heavy line represents the theoretical equation $-\log f = 1{\cdot}00\sqrt{\mu}$.

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$[Co(NH_3)_4C_2O_4]^+[Co(NH_3)_2(NO_2)_4C_2O_4]^-$	$s = 4{\cdot}9 \times 10^{-4}$
$[Co(NH_3)_4(NO_2)(CNS)]^+[Co(NH_3)_2(NO_2)_4C_2O_4]^-$	$s = 3{\cdot}3 \times 10^{-4}$
$[Co(NH_3)_4C_2O_4]_2^+[S_2O_6]^=$	$s = 1{\cdot}5 \times 10^{-4}$
$[Co(NH_3)_6]^{+++}[Co(NH_3)_2(NO_2)_4C_2O_4]_3^-$	$s = 5{\cdot}0 \times 10^{-4}$

The saturated solutions were obtained by the simple expedient of letting the solvent trickle slowly down a long vertical tube packed with crystals, a method which had been used by Brönsted much earlier in his measurements on rhombic and monoclinic sulphur. In spite of the low solubilities involved, an accuracy of about 0·3% was attained, as may be seen from Figure 1. The line drawn represents the predictions of the Debye–Hückel theory, which are clearly followed very closely.

The cobaltammines also played a considerable part in the development of Brönsted's ideas on acids and bases, and there is one other example of their use which may be mentioned here. On a simple electrostatic picture the solubility of a salt in different solvents should be a smooth

function of the dielectric constant, but this is not so in practice, no doubt largely because of the part played by non-electrostatic factors. In a paper given to the 1931 meeting of the British Association Brönsted reported solubility measurements on the two substances $Co(NO_3)_3(NH_3)_3$ and $[Co(NO_3)_3(NH_3)_4]^+[Co(NO_3)_4(NH_3)_2]^-$ which contain exactly the same chemical groupings, but are respectively a non-electrolyte and a uni-univalent salt. By considering the ratio of the solubilities of these two substances, rather than the solubility itself, he hoped to eliminate the non-electrostatic factors, and he did in fact find a fairly regular behaviour for nine solvents with dielectric constants ranging from 21 to 84.

Apart from electrolytes, a particular thermodynamic problem which interested Brönsted from 1930 onwards is the effect of molecular size on thermodynamic properties. He carried out experiments on the solubilities and distribution between phases of molecules (or colloidal particles) which were chemically very similar, and differed mainly in size. These led him to the concept of an "isochemical series," and he established several laws governing the solubilities and other properties of such a series. Although he did not realise that large entropy effects might be present in mixtures of molecules of different sizes, Brönsted's laws are essentially the same as those developed recently for high polymers such as rubber. Some of Brönsted's last published work was on the vapour pressures of mixtures of the normal paraffins, for which he obtained experimental results of very high accuracy, and established some new regularities which have not yet been explained theoretically. This work contains some very neat experimental devices: for example, in order to weigh a vessel containing liquid and vapour without detaching it from the rest of the apparatus, he suspended it from an ordinary balance and used as a connecting tube such a fine glass capillary that it had little effect within the sensitivity of the balance.

Brönsted's work on isochemical series is of particular interest, because it represents one of the few cases in which he gave a molecular interpretation for the laws which he had established experimentally. In general he was curiously reluctant to consider any detailed molecular picture, preferring to derive from experiment empirical regularities which should be independent of any particular features of the molecules concerned. For example, one sometimes felt that he regretted the mechanistic explanation given by the Debye–Hückel theory for the laws which he had established experimentally, and other examples of a similar attitude will be given later. I well remember his indignation when I suggested to him, shortly before his death, that a statistical approach was helpful in explaining the laws of thermodynamics to students.

Certainly there was no suggestion of any molecular interpretation in his writings on the fundamental bases of thermodynamics, which occupied him to an increasing extent during the last ten years of his life. Although he criticised severely the conventional approach to the Second Law, his treatment remained a strictly phenomenological one. It is difficult to give an estimate of the value of this work, and I shall not attempt to summarise its content here. It roused violent controversy in Denmark, but has received little attention elsewhere: it is usually regarded as formally correct, but rather sterile. It is true that a similar view was at one time held about Brönsted's acid–base definition, which proved to have such a widespread importance, and it would indeed be interesting if his concepts of heat and entropy should eventually prove equally fruitful. They may perhaps be helpful in treating processes in which a steady state is set up by the irreversible flow of energy or matter through the system, a field which Brönsted had begun to study experimentally shortly before his death.

The second main field of Brönsted's activities was reaction kinetics, and in particular catalysis by acids and bases. This interest arose comparatively later in Brönsted's scientific development, but is probably the work for which he is best known, especially outside Denmark. It was closely connected with his work on electrolytes, and it is difficult to trace the exact order in which the various interwoven ideas arose, since papers on both kinetic and thermodynamic topics followed one another with bewildering rapidity in the nineteen-twenties.

Brönsted first used kinetic measurements in 1921 in connection with the effect of salts on acid–base equilibria. He was particularly concerned to show that the effect of salt concentration on hydrogen-ion concentration depends on the nature of the equilibrium involved: for example, in the system

$$CH_3{\cdot}CO{\cdot}OH \rightleftharpoons CH_3{\cdot}CO{\cdot}O^- + H^+$$

the hydrogen-ion concentration will be increased by added salt, while the equilibrium

$$NH_4^+ \rightleftharpoons NH_3 + H^+$$

will be little affected by salt additions, and in the system

$$[Fe(H_2O)_6]^{+++} \rightleftharpoons [Fe(H_2O)_5OH]^{++} + H^+$$

the hydrogen-ion concentration will be decreased by addition of salt. These results follow directly from the Debye–Hückel expression for activity coefficients, but were derived by Brönsted from the experimental evidence on the activity coefficients of ions of different charges. In order to test his conclusions it was necessary to measure the hydrogen-ion concentrations in these solutions, and for this purpose he used the rate of reaction of diazoacetic ester with water to give glycollic ester and nitrogen, a well-known example of hydrogen-ion catalysis. This at once raised questions of fundamental importance, for it was held in many quarters that the reaction velocity in such a system was proportional to the activity rather than to the concentration of hydrogen ions. Brönsted showed definitely that the concentration was the appropriate quantity: for example, when only a strong acid is present, the effect of added salt on the reaction velocity is much less than its effect on the hydrogen-ion activity. This justified the use of the diazoacetic ester reaction for measuring hydrogen-ion concentrations, and the salt effects observed with solutions of weak electrolytes agree with those predicted from activity data. This type of kinetic salt effect, depending on the displacement of an equilibrium, was termed by Brönsted a "secondary salt effect."

There existed at the time a mass of unco-ordinated data on the effect of added salts on reaction velocities, including many reactions involving only strong electrolytes, where no secondary salt effect could be involved. In this latter class of reaction it is customary to speak of "primary salt effects." Brönsted next showed in 1922 that all the existing data for primary salt effects could be summarised by the following simple statement: reactions between ions of like charge exhibit a large positive salt effect, reactions between ions of unlike charge a large negative salt effect, and reactions between an ion and a neutral molecule a small salt effect which may be either positive or negative. This classification was in itself a great step forward, but Brönsted gave it a further interpretation in terms of his famous expression for the effect of environment on the rate of a chemical reaction. For a reaction between two species A and B the expression for the reaction velocity v is

$$v = k[A][B]\frac{f_A f_B}{f_X} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k is independent of environment, f is an activity coefficient, and X represents the "critical complex" of A and B through which they must pass in order to react. It now seems obvious to us that the correct expression must involve the activity coefficient of some intermediate complex, as well as those of the reacting species, but Brönsted was the first to realise this, though the concept of a critical complex had previously been employed by Marcellin. We know very little about the nature of X, but we do know that its charge is the algebraic sum of the charges on A and B, and this is sufficient to predict approximately how its activity coefficient will vary with salt concentration. Nowadays this prediction would be made on the basis of the Debye–Hückel theory, but Brönsted again had to use the experimental data available for ionic activity coefficients, and was able to show that equation (1) corresponds to the rules for the salt effect given above, and agrees approximately with the magnitude of the observed effects. In particular it shows that in a reaction involving an ion and a neutral molecule (such as the decomposition of diazoacetic ester ion in presence of hydrogen ions) the activity coefficient factor will be near to unity, and hence the reaction velocity will be proportional to the concentrations of ester and hydrogen ions, and not to their activities. After the advent of the Debye–Hückel theory Brönsted made more measurements on salt effects in very dilute solutions, and found a complete confirmation of equation (1). It is interesting to note that Brönsted did not attempt to give any detailed molecular explanation of this equation, and the semi-thermodynamic derivation which he gave in 1922 was not made much clearer by a more detailed treatment in 1925. Brönsted's equation is now of course regarded as a special case of the transition-state expression for reaction velocity, but Brönsted himself showed little interest in later developments in this field.

The second major advance which served to clarify a large mass of kinetic work was Brönsted's extended definition of acids and bases, first published in 1923. Identically the same definition was put forward almost simultaneously by Lowry in this country. This definition is now generally accepted: it states that *an acid is a species which has a tendency to split off a proton, and a base is a species which has a tendency to add on a proton.* All acids and bases can therefore be arranged in conjugate or corresponding pairs according to the scheme

$$A \rightleftharpoons B + H^+$$

This definition of acids includes not only uncharged molecules such as $CH_3{\cdot}CO_2H$, but also anions like HSO_4^-, $HPO_4^=$ and cations like NH_4^+, $[Fe(H_2O)_6]^{+++}$. The new definition of bases was even

more fruitful, since there had previously been great confusion, for example as to whether the ammonia molecule or the hypothetical ammonium hydroxide should be regarded as a true base. The Brönsted–Lowry definition includes uncharged bases like NH_3, NMe_3 and anion bases such as $CH_3{\cdot}CO{\cdot}O^-$, OH^-, CO_3^{--}. It was not so easy to find an example of a cation base, but once again the cobaltammines and similar compounds came to the rescue: for example the ion $[Co(NH_3)_5(H_2O)_4OH]^{++}$ is a base in virtue of the reaction

$$\underset{\text{Base.}}{[Co(NH_3)_5(H_2O)_4OH]^{++}} + H^+ \longrightarrow \underset{\text{Acid.}}{[Co(NH_3)_5(H_2O)_5]^{+++}}$$

It is immediately clear that the hydroxyl ion is not in any way unique, since it is only one member of a whole class of anion bases. On the other hand the hydrogen ion does appear to occupy a privileged position as long as we write it as H^+, *i.e.*, a bare proton. However, following Fajans and others, Brönsted realised that the free proton could not exist in any significant concentration in the presence of other molecules, and that in aqueous solution it existed as the hydroxonium ion, H_3O^+, entirely analogous to the ammonium ion, NH_4^+. In fact, the "hydrogen ion" is a different entity in each solvent, in each case being only one of a class of cation bases.

Once the claim of hydrogen and hydroxyl ions to uniqueness has been abandoned, it becomes possible to write all the reactions of acids and bases (variously described as dissociations, neutralisations, hydrolyses, buffer systems, etc.) in the symmetrical form:

$$\text{Acid (1)} + \text{Base (2)} \rightleftharpoons \text{Base (1)} + \text{Acid (2)}$$

Some examples of this are given in the following table, and a similar set could be given for non-aqueous solvents.

A_1	+ B_2	$\rightleftharpoons$ A_2	+ B_1	Description.
$CH_3{\cdot}CO_2H$	H_2O	H_3O^+	$CH_3{\cdot}CO{\cdot}O^-$	Dissociation in water *or* buffer action in acetic acid + acetate.
$CH_3{\cdot}CO_2H$	NH_3	NH_4^+	$CH_3{\cdot}CO{\cdot}O^-$	Dissociation of acetic acid in liquid ammonia, *or* dissociation of ammonia in glacial acetic acid, *or* neutralisation of $CH_3{\cdot}CO_2H$ by NH_3, with or without solvent.
H_2O	$CH_3{\cdot}CO{\cdot}O^-$	$CH_3{\cdot}CO_2H$	OH^-	Hydrolysis of acetate solutions.
NH_4^+	H_2O	H_3O^+	NH_3	Hydrolysis of ammonium salts, *or* buffer action in $NH_3 + NH_4Cl$.
H_2O	HPO_4^{--}	$H_2PO_4^-$	OH^-	Hydrolysis of secondary phosphates.
H_2O	NH_3	NH_4^+	OH^-	Dissociation of ammonia in water.
$H_2PO_4^-$	H_2O	H_3O^+	HPO_4^{--}	Dissociation of primary phosphate *or* buffer action in mixtures of primary and secondary phosphate.

Since the hydrogen and hydroxyl ions are not unique among acids and bases, there is no reason why they should have the monopoly of catalytic cation in chemical reactions, and Brönsted's next important contribution was the experimental demonstration of *general acid–base catalysis* in a number of reactions. Brönsted and Pedersen's paper on the nitroamide decomposition, published in 1924, showed that the reaction was catalysed by the following classes of base:

(1) Anion bases like acetate ion, oxalate ion, etc.
(2) Uncharged bases like aniline and pyridine.
(3) Cation bases like $[Co(NH_3)_5OH]^{++}$.

Brönsted and Pedersen made a detailed study of catalysis by anion bases, and later papers (1925—34) extended this to the other types of base and also to non-aqueous solvents. The mutarotation of glucose offered rather more complications, since it is catalysed by both acids and bases. Thus in an acetate buffer solution the full expression for the reaction velocity is

$$v = k_0 + k_1[H_3O^+] + k_2[OH^-] + k_3[HOAc] + k_4[OAc^-]$$

However, by carefully designed experiments it was possible to separate out the effects of different species, and the 1927 paper by Brönsted and Guggenheim demonstrated the catalytic effect of anion bases, uncharged bases, cation bases, uncharged acids like acetic acid, and cation acids like the ammonium ion. Very similar conclusions were published by Lowry in the same year, though his investigations were less complete.

The idea of catalysis by species other than hydrogen and hydroxyl ions was not altogether a new one, and in particular the "dual theory," suggested by Acree, Snethlage, and H. S. Taylor, had assumed catalysis by undissociated acid molecules. However, most of their deductions

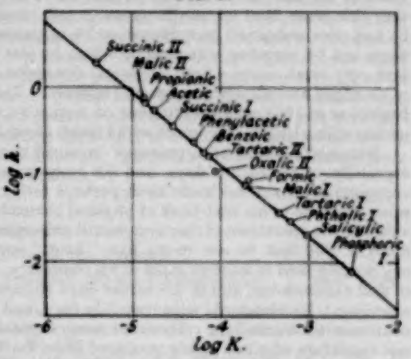
were based upon incorrect values for the degree of dissociation of electrolytes, and did not allow for primary and secondary salt effects. In his monograph on "acid–base catalysis" (published in Danish in 1926, English translation in 1928) Brönsted devoted a good deal of space to a severe criticism of this earlier work, and was in fact able to show that in almost all cases the supposed catalytic effect of acid molecules was based on a misinterpretation of the data, or could reasonably be attributed to a salt-effect. The only notable exception to this statement was Dawson's work on the acetone–iodine reaction, and here Brönsted's strictures were rather less than just. It is true that Dawson did not take into account recent views on electrolytes and that his experiments were planned in such a way as to involve complicated salt-effects. Nevertheless, there is no doubt that his work definitely establishes catalysis by carboxylic acid molecules, and in fact still provides the most extensive set of data for this type of catalyst, although his numerical values need some revision in the light of modern developments.

If we consider a series of similar acids and bases, it is natural to expect that their catalytic power for a given reaction will depend on their acidic or basic strength. In his first paper on the nitroamide decomposition Brönsted gave a quantitative form for this dependence which has been found to be generally valid, and which is commonly known as the "Brönsted relation." For basic catalysis it can be written in the form:

$$k_b = GK_b^{\alpha}$$

where k_b is the catalytic coefficient of a base of dissociation constant k_b, and G and α are constants characteristic of the reaction, the temperature, and the solvent, α being less than unity. Figure 2 shows how well this relation is obeyed for the anion-catalysed decomposition of nitroamide: for most other reactions the agreement is rather less good. As in many other cases Brönsted arrived at the form of this relation primarily by considering the experimental data. The only theoretical basis which he gave for it was a vague and unsatisfactory one, and he was not particularly interested in later attempts to interpret the relation in terms of molecular potential-energy curves.

FIG. 2.



The relation between catalytic effect and acid–base strength for the anion-catalysed decomposition of nitramide.

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I must now attempt some kind of summing up of Brönsted as a scientist and as a man. His skill as an experimentalist was not immediately apparent because of the simple nature of many of his methods, and it took some time to realise how much skill and discrimination lay behind an apparently simple piece of experimental work. His great strength lay in the choice of the most suitable substance or reaction, and in the planning of a series of experiments to attain the desired end with the greatest certainty and economy. For this reason his researches always had a much wider application than the immediate purpose in hand, and one of the greatest benefits of working with him was the opportunity of sharing his insight into general methods and planning of research. Many of his pupils have modelled their subsequent work on Brönsted's prototypes: for example, most later work on activity coefficients from solubility measurements and on general acid–base catalysis follows closely on some lead originally given by Brönsted.

It is more difficult to place Brönsted as a theoretical physical chemist in relation to the main developments of his time. We have already seen several examples of his absorption in thermodynamics and his love of an experimental approach, and the adjective "classical" seems an appropriate one to describe his contributions to physical chemistry. In the field of solutions his work has had a clarifying effect to which it is difficult to find a parallel. Although his mind was a most agile one, several of the major trends in modern physical chemistry failed to rouse his interest: for example, the experimental and theoretical study of molecular structure, and the theoretical treatment of reaction velocities. Looking back, it seems strange that one of the greatest investigators of reaction kinetics in solution should never have deliberately measured an activation energy. On the other hand, there is no doubt that this limitation

of interest enabled him to attack his chosen field with greater intensity and singleness of vision.

Brönsted was an individualist in his work, and owed little to the influence of other scientists, though the tradition of Julius Thomsen fostered his early interest in thermodynamics, and his training under S. M. Jörgensen introduced him to the cobaltammines and gave him high standards of preparative and quantitative work. There is only one instance where he collaborated with another scientist outside his own field, and that was in his famous work with Hevesy on the separation of the isotopes of mercury and chlorine by ideal distillation at low pressures. In his earlier days he had few junior collaborators, but in the period 1922—37 many chemists from other countries, particularly England and the United States, went to work with him. I myself spent four years in his laboratory, and I remember very clearly the impression of integrity and intensity of scientific endeavour which I received. One guest worker described his laboratory as a place of "high chemical potential," and the phrase does give something of the tense and personal feeling which Brönsted inspired. He showed great kindness and consideration to his collaborators from overseas, and the subsequent work done by many of them shows the lasting effect of his influence. On first acquaintance he seemed rather reserved, but one soon realised that this arose from an unwillingness to talk carelessly or lightly on scientific matters. When he had once embarked on a discussion his acuteness and remorseless logic were remarkable, and there can be very few occasions on which he was worsted in a scientific argument. He did in fact very much enjoy a keen polemical discussion, and never hesitated to express his criticisms in an edged and sometimes personal manner. This involved him in a number of controversies, beginning in 1908 with his criticism of Nernst's concept of "ideal concentrated solutions," and ending with a lengthy argument with Danish physicists about the foundations of thermodynamics.

Brönsted's duties as a professor involved a considerable amount of elementary teaching, especially in his earlier days, and his lectures were elegant in delivery and content. Their concentrated exactness made them perhaps rather indigestible for the average student, and the same was true of his text-book of physical chemistry. The later editions of this book incorporated his own treatment of thermodynamic principles, and we can sympathise with the polytechnic student who had to use terms like "heat" and "work" in one sense in his physics and engineering, and in another sense in his chemistry. The Danish system involves a large amount of oral examination, and in his earlier days Brönsted gained some reputation for severity as an examiner: his standards were certainly high, and he was not much given to compromise, least of all in scientific matters. There are many anecdotes about these examinations, and I remember one candidate who had rashly professed some knowledge of the occurrence and properties of the silicates, and who was finally driven by Brönsted's remorseless logic into maintaining that a paving-stone would probably dissolve completely if stirred up with a little water! However, as he became older Brönsted became more lenient towards his younger students, though he could still be a formidable opponent to candidates for the doctorate degree.

In private life Brönsted had great personal charm and a wealth of interests outside his science. The chief of those was his love of the countryside and its people, which remained with him all his life. His family holidays were usually spent in some remote part of the country, and he had a very extensive knowledge of Danish wild life, especially of birds. It is interesting to note that his last publication, just before his death, was a note describing some observations on insect behaviour made during his summer holiday. He felt very keenly about the preservation of natural beauty and nature reserves, and took a prominent part in campaigns to this end. Music and painting were also among his accomplishments, and through his marriage he came into close contact with many of Denmark's leading artists and musicians. He had a wide knowledge of literature in several languages and a remarkable gift not only for accuracy but also for elegance in expression in both Danish and English.

Brönsted travelled widely in Europe, and made several visits to the United States. In spite of his strong Danish patriotism he had a great deal of sympathy and understanding for other countries, and especially for England. His early contacts were mostly with German scientists, but after the First World War his sympathies turned decisively towards this country. In 1920 he spent several months in England, mainly with Professor Donnan at University College, and he made at least seven more visits before 1939, including several to attend meetings of the Faraday Society. Among many other honours he was made an honorary member of the Academy of Arts and Sciences in 1929, an honorary Fellow of the Chemical Society in 1935, and an honorary doctor of London University in 1947.

The Second World War served only to strengthen the ties which bound him to English things and English people, and he never had any doubts as to the rightness or the eventual outcome

of the struggle. From the first day of the German occupation he spent several hours daily listening to the broadcast news from London, and he also read widely in English history and biography: when I visited him in 1945 he still had on his table a list of English Foreign Secretaries from 1769 onwards. The occupation also turned his attention to public affairs in general, in particular the vexed question of Schleswig and the Danish–German frontier, about which he spoke and wrote in his usual forthright manner. Nevertheless, it was a surprise to many of his friends when in 1947 he accepted nomination as a candidate for the Danish parliament, and a still greater one when on October 28th he was elected. He took this responsibility seriously, and immediately began to study parliamentary procedure, but he was overtaken by his last fatal illness before he could take his seat, and died on December 17th. It is interesting to speculate how he would have fared in Parliament and how his logical and uncompromising mind would have dealt with the half-truths of politics. He himself believed that many of the ills of mankind were due to the lack of logic and precise definition in public affairs, and it is an open question whether the application of this principle would have brought success or frustration.

It is very fortunate that Brönsted was able to visit England again in the summer of 1947, when he attended the Chemical Society Centenary celebrations and the International Congress. He enjoyed this visit to the full: not only the formal scientific occasions, but also the quieter times which he and Mrs. Brönsted spent in the homes of their English friends, and by themselves in a remote corner of the English countryside. It was a great shock to hear of his sudden death so soon afterwards, and many people in many countries will mourn him, not only because of his contributions to science or for his inspiring personal genius, but also as a fine and lovable person. Many of his ideas have passed into the common currency of physical chemistry, and, although one hesitates to predict the future of any scientific subject, it is difficult to imagine a state of affairs in which they would not still be valid and useful. This society has done itself a great honour by numbering him among its Honorary Fellows.

R. P. Bell.

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Newer Developments of the Chemistry of Many-membered Ring Compounds.

CENTENARY LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY IN LONDON ON FEBRUARY 17TH, 1949.

By V. PRELOG.

I AM able to speak about the newer developments of the chemistry of macrocyclic compounds thanks to the fortunate circumstance that I am working in the Laboratory of organic chemistry at the Institute of Technology in Zürich. In this laboratory the many-membered rings were discovered by L. Ruzicka and the fundamental analytical and synthetical work has been done on this interesting group of compounds. Ruzicka himself lectured on his work before the Chemical Society in London almost exactly 15 years ago.[1] The most important theoretical consequences of these investigations and especially their influence on the so-called strain theory form part of general text-book chemistry to-day. Moreover, the perfume industry could not dispense with the artificial musk-like scents, which became available through this work.

In spite of the wide extent of this field only few laboratories have devoted themselves to the chemistry of many-membered ring compounds. I would like to mention, in addition to the Zürich Laboratory and a connected group led by M. Stoll in Geneva, Carothers, Adams, and Blomquist in America, and Ziegler, Lüttringhaus, and Hunsdiecker in Germany. If I concern myself mostly with the newer work of our own group, it is only on account of restricted time.[2] For the same reason I cannot deal now with the very interesting recent work on many-membered ring peptides, antibiotics, and alkaloids.

The reason why the chemistry of many-membered ring compounds was not more intensively studied lay in their difficult accessibility. In the heroic age, Ruzicka and his co-workers prepared the many-membered ring ketones, which they used as starting materials for other compounds of this group, by dry distillation of the rare-earth salts of dicarboxylic acids.[3] In favourable cases the yields reached a few per cent. The introduction of the dilution principle by K. Ziegler, H. Eberle, and H. Ohlinger [4] did not make the many-membered ring derivatives readily available, since the technique of ring-closure in great dilution is rarely simple. All general procedures for the preparation of macrocyclic compounds had still another important disadvantage. The compounds of medium ring-size, containing 8 to 12 members, could be prepared only in disappointingly low yields of a few tenths per cent.

The introduction of the very advantageous acyloin synthesis,[5] which allows preparation in very good yields of ring compounds having more than 8 members, formed therefore a starting point for new approaches to this field. This synthesis leads from easily accessible dicarboxylic acid esters in a simple way without using great dilutions to macrocyclic acyloins, which can be converted easily into various other cyclic compounds. The following formulæ show a variety of reactions, which were carried out recently:

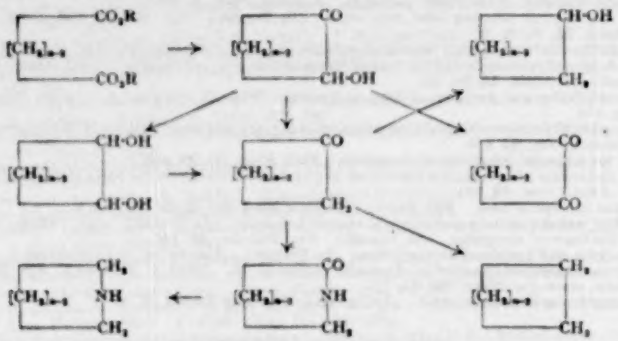
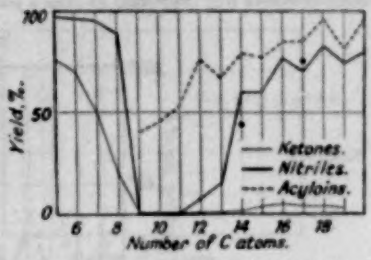


Fig. 1 illustrates the dependence of yield on ring size for the three most important general procedures for the preparation of many-membered ring compounds: the preparation of ring

ketones according to Ruzicka, the preparation of imino-nitriles by Ziegler's method, and the acyloin procedure. One can see that it is now possible to obtain ring-compounds of every size in reasonable yield. In this way the field of many-membered ring-compounds became a real playground for the organic chemist. The acyloin procedure leads to the democratisation of this hitherto very aristocratic group of compounds. It is now no more difficult to obtain *cyclo*-decanone than any higher aliphatic ketone.

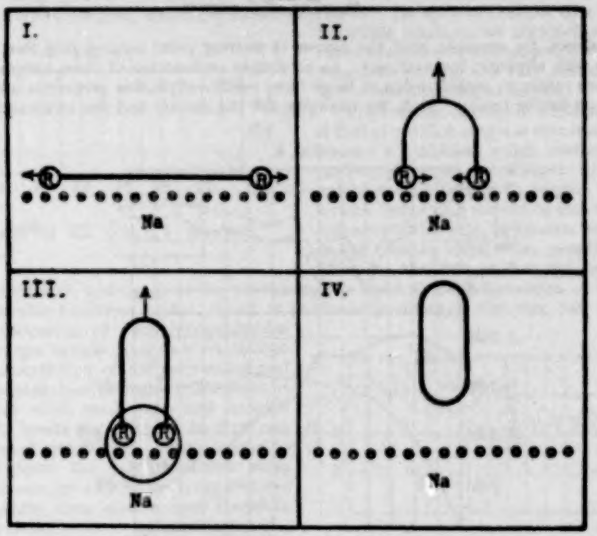
FIG. 1.



A very elegant application of the acyloin synthesis to a macrocyclic compound is exemplified in the synthesis of civetone by M. Stoll, J. Hulstkamp, and A. Rouvé.[6] It was possible to synthesise both *cis*- and *trans*-isomers of civetone and this is the first case of a double bond incorporated in a ring in both *cis*- and *trans*-configuration in known fashion.

The problem of the surprisingly good yields of many-membered ring acyloins obtained from the acyloin synthesis in concentrated solutions is explained by our reaction mechanism shown schematically in Fig. 2.[7] The two electrophilic carbon atoms at the ends of the chain of a dicarboxylic acid ester are first adsorbed by the electron-covered surface of the molten sodium. So far as the flexibility of the carbon chain allows, the electrophilic residues can slide over the metal surface and can thus approach each other. As less energy is necessary

FIG. 2.



$$-\overset{\overset{OCH_3}{|}}{\underset{|}{C}}=O \longrightarrow -\overset{\overset{OCH_3}{|}}{\underset{+}{C}}-ONa \longrightarrow -\underset{++}{C}-ONa + NaOCH_3$$

for this than for splitting the molecule off the surface, the collisions of the adsorbed molecule with other molecules lead to the approach of the terminal carbon atoms and finally to the ring closure. After the ring closure the molecule no longer possesses electrophilic centres and is therefore no longer bound to the surface.

The work on many-membered rings was from the beginning carried out with two motives,

the one practical—the preparation of musk-like perfumes—and the other theoretical—the investigation of the influence of ring size on the physical and chemical properties. It seemed that this second aim would not have much interest since according to older views the higher unstrained ring homologues of *cyclo*hexane should not differ from it more than the higher aliphatic homologues differ from the lower. In fact *the physical and the chemical properties of the many-membered ring compounds do show a peculiar and unexpected dependence on ring size.*

FIG. 3.

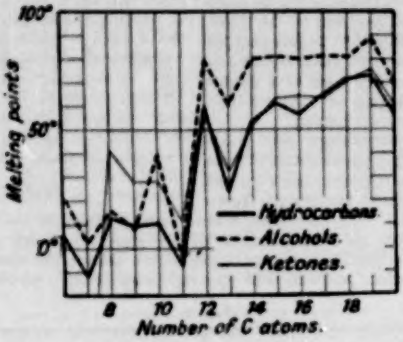
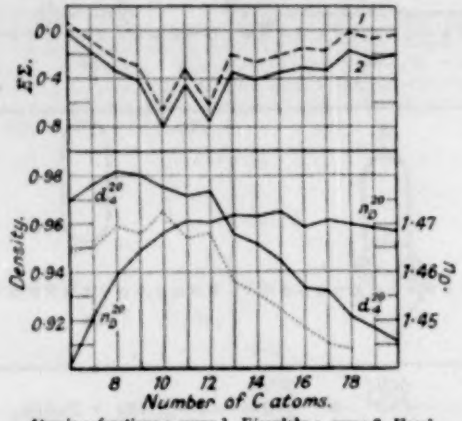


Fig. 3 shows, for example, that the curves of melting point against ring size do not rise steadily as with aliphatic homologues.[6] As no simple explanation of these curves is possible we shall turn rather to consideration of those more readily explicable properties which are not dependent on lattice forces. Such, for example, are the density and the molecular refraction

FIG. 4.



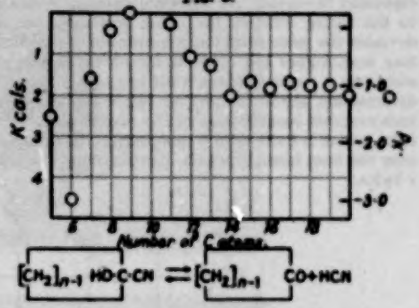
Atomic refractions: curve 1, *Eisenlohr; curve* 2, *Vogel.*

in the liquid state. Most of the investigated series of alicyclic many-membered ring compounds show a maximum of density and a depression of molecular refraction at medium ring size. In this manner they differ from the aliphatic homologous series, which show a steady increase or decrease of density and no appreciable deviation $E\Sigma$ from the calculated molecular refraction.

Fig. 4 describes the above-mentioned properties as a function of ring size in the series of cyclanol acetates.[9] Cyclanol acetates are specially suitable for such measurements, because the whole series is liquid at room temperature so that no corrections are necessary.

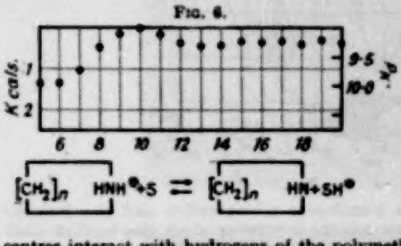
To the extreme values of the physical properties correspond extreme values of the chemical properties of the medium-size ring compounds. As the first example of the chemical properties, the dependence of the equilibrium constants on ring size is shown in Fig. 5 for the reaction between cyclanones and hydrogen cyanide in alcoholic solution.[9] The negative logarithms of the dissociation constants and the free energy of the reaction are plotted against ring size, the influence of which is unexpectedly great. The two extreme values lie on the limits of possible experimental determination. That means that *cyclo*hexanone cyanohydrin scarcely dissociates at all, whereas *cyclo*decanone does not add on hydrogen cyanide. For comparison, the dissociation constant for dioctyl ketone cyanohydrin is given on the right-hand side of the graph.

Fig. 5.



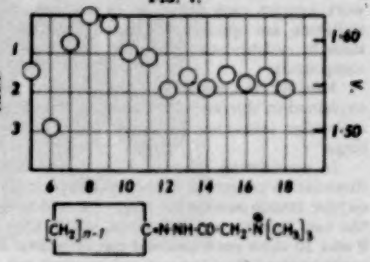
As a further example of the dependence of an equilibrium constant on the ring size we can consider the dissociation constants of polymethylene-imines shown in Fig. 6.[10] We also measured polarographically the half-wave potentials for the cathodic reduction of the Girard-T derivatives of cyclic ketones, which are shown on Fig. 7.[11] In spite of the fact that it is not a reversible reaction, we obtained a shape of curve which shows a dependence of half-wave potentials on ring size very similar to those in the two foregoing examples.

Fig. 6.



The common feature in all these reactions is that at medium-ring size that reaction component is stabilised which contains a more nucleophilic oxygen or nitrogen: for example, ketone is stabilised with respect to cyanohydrin, imine with respect to the corresponding ammonium salt, hydrazone with respect to the reduced form. One possible explanation for this fact is that the nucleophilic centres interact with hydrogens of the polymethylene chain through formation of some kind of intramolecular hydrogen bridge, which is particularly strong if the ring has a medium size. The formation of such intramolecular hydrogen bridges in only possible if we assume a certain constellation of the poly-membered ring. As constellation we define those forms of the molecules which result from free rotation around single bonds, for example, the chair and the boat form of *cyclo*hexane. With respect to stability of form, the poly-membered rings stand in between the rigid small rings and the mobile aliphatic open chains, and therefore these compounds provide an interesting material for studies of the influence of constellation on chemical and physical properties. The following two factors will determine mainly the energy and the probability of a constellation: first, the van der Waals radii of the atoms, which are well illustrated by Stuart models, and secondly, such interactions as are not shown by atomic models—that is, forces not expressed in classical formulæ, for instance, those which restrict rotation around a single bond in aliphatic compounds in contradiction to the views of classical stereochemistry.[12] These forces cause the inequality

Fig. 7.



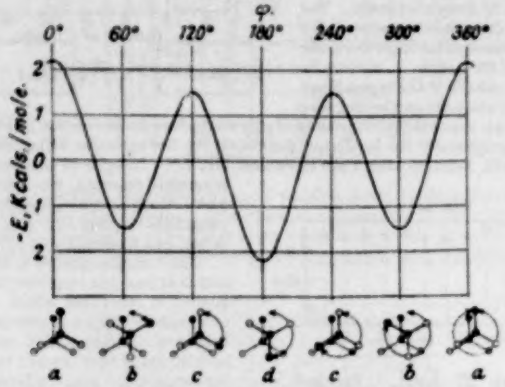
of various constellations of a polymethylene chain from the energetics standpoint. The changes of the potential energy of a chain of four methylene groups around the central C–C bond can be described approximately by the formula [13]

$$E = -1{\cdot}7\cos\phi - 0{\cdot}5\cos\phi \text{ kcals. per mole.}$$

This function is shown together with corresponding configurations in Fig. 8.

Two constellations *b* and *d*, which are separated from each other by energy barriers, are especially favoured. In a normal paraffin hydrocarbon the constellation *d*, which corresponds to the zigzag form of the chain, predominates. In *cyclo*-paraffins the polymethylene chain deviates the more from the constellation *d* the smaller the ring. In *cyclo*pentane and its lower ring homologues the chain is forced by ring strain into the energetically unfavourable constellation *a*. *cyclo*Pentane itself has, according to K. S. Pitzer,[14] a non-planar form because the deformation of the tetrahedral valency angles of the non-planar form is less serious than the unfavourable constellation of the planar form. From this it is understandable that the chair form, which is built from 6 energetically favourable constellations, predominates in *cyclo*hexane over the boat form, in which constellation *b* occurs 4 times and the unfavourable constellation *a* twice.

FIG. 8.



These considerations being transferred to homologous *cyclo*-paraffins and simultaneous account being taken of van der Waals radii, one has the interesting result that medium-sized rings with 8—12 members can only be built from less favourable constellations. In contrast to this, the chains of the higher *cyclo*-paraffins can again be constructed from energetically favourable constellations *b* and *d*. Just as in small rings classical strain and constellation work against each other, so in medium-sized rings van der Waals repulsive forces and constellation are opposed. The medium-sized rings suffer a greater interaction between atoms than in *cyclo*hexane: they are therefore at a higher energy level than unbranched aliphatic compounds.

Maxima and minima in the physical properties of medium-sized ring compounds may be explained in this way, for example, the reduction of electron polarisability and consequently of molecular refraction by the stronger interaction of non-adjacent atoms in the medium-sized rings.

In considering the influence of ring size on the chemical properties, for example, on the dissociation constants of the cyanohydrins, it should be realised that in small-ring ketones the oxygen stands outside the ring. In medium-sized rings we have many possible forms in between the two extreme constellations, which may be termed "O-outside" and "O-inside." Figs. 9 and 10 show such extreme constellations for *cyclo*decanone. The O-outside constellation of medium-sized ring ketones are marked out, first, by a more favourable constellation of the polymethylene chain,* and secondly, by an intramolecular interaction between the carbonyl

* In the model shown by Fig. 9 we have 6 times the unfavourable constellation *c* and twice the favourable constellation *b*. If the oxygen atom is outside the ring, as in the model shown by Fig. 10, the unfavourable constellation *c* occurs 8 times.

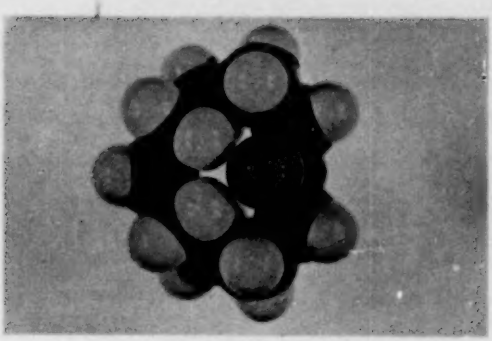


FIG. 9.

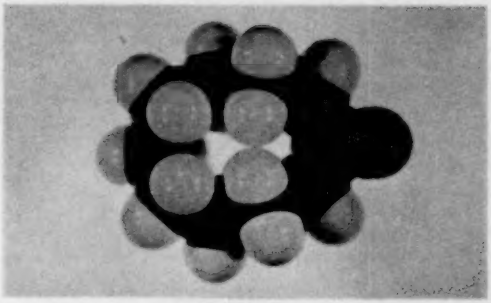


FIG. 10.

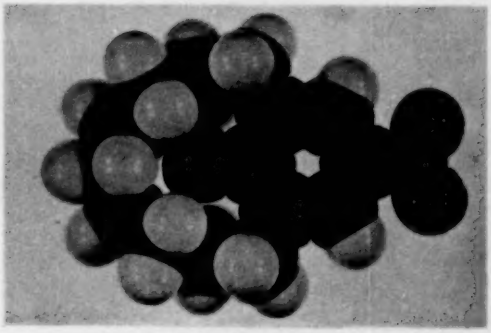


FIG. 11.

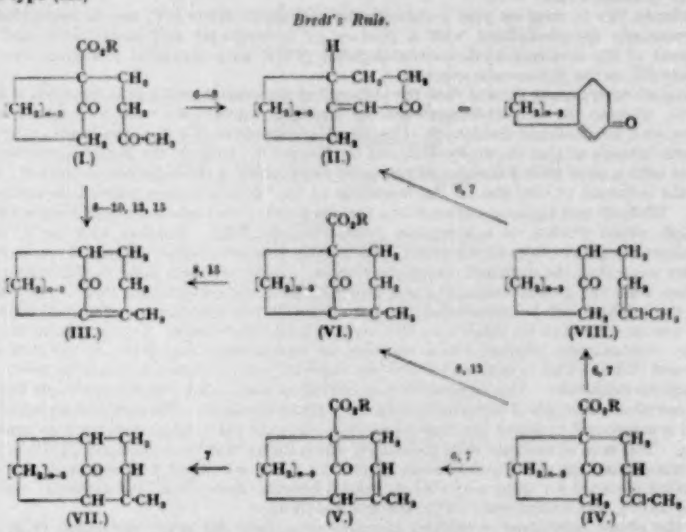
[*To face p.* 434.

oxygen and the hydrogens of the polymethylene chain; the distance between these atoms is especially small in medium-sized ring ketones. The interaction is stronger in the ketone than in the cyanohydrin and stabilises the former, as was found experimentally. Very similar considerations can be developed for the other reactions mentioned.

In an attempt to prove the consequences of the " O-inside " configuration of cyclanones, Dr. Günthard studied the infra-red absorption spectra. As expected, the frequency of C=O bond-stretching band was smaller with a medium-ring ketone than in *cyclo*hexanone or a large-ring ketone. The following values (in $cm.^{-1}$) were obtained in the liquid state: *cyclo*hexanone 1710, *cyclo*octanone 1692, *cyclo*nonanone 1698, *cyclo*decanone 1694, *cyclo*undecanone 1700, *cyclo*dodecanone 1697, *cyclo*tridecanone 1707.*

In addition to the physical and physicochemical methods of approach, we tried to examine the question of the constellation of many-membered ring compounds by the classical methods of organic chemistry. Assuming that the rate of ring closure is influenced by constellation, it should be possible under favourable conditions to obtain information about the constellation of a monocyclic compound by transforming it into a bicyclic compound. We carried out a series of such experiments and found some facts which deserve brief mention.

Robinson and his co-workers [18] showed that condensation of the *cyclo*hexanonecarboxylic esters with quaternary bases of dimethylaminobutanone (" Mannich base ") gives compounds, which can be simultaneously saponified, decarboxylated, and cyclised to αβ-unsaturated octalones. We obtained analogous products (II) by condensing the cyclic β-keto-carboxylic esters (I) containing a 7- or an 8-membered ring.[19] In the case of the 8-membered ring we isolated a second isomeric αβ-unsaturated ketone (III), in which the carbonyl of the side chain had condensed with the active methylene group in the ring. The two isomers could be separated easily by making use of the fact that the second of them does not give the carbonyl group reactions, for example, does not react with Girard reagent-T. Ultra-violet absorption spectra and Kuhn–Roth oxidation provide evidence for the constitution. The compound with the bicyclic system condensed in the 1 : 2-position has an absorption maximum at a shorter wavelength and gives no acetic acid by oxidation, whereas the isomer with the bicyclic system condensed in the 1 : 3-position gives one molecule of acetic acid by oxidation and absorbs at longer wave-length. Using higher homologues of *cyclo*octanonecarboxylic ester, we got only products of the type (III)



* Dr. G. B. B. M. Sutherland, Cambridge, who independently investigated the infra-red spectra of some cyclanones observed in *cyclo*octanone changes in the frequencies of the C=O band at about 5·7 μ. as well as of the C–H band at about 1·75 μ., which indicate an intramolecular hydrogen bond.

These experiments permit some definition of the limits of validity of Bredt's rule, which states that in bridged-ring systems a double bond cannot start from a bridgehead. Fundamentally, Bredt's rule expresses the requirement of effective overlap of the *p*-electron orbitals constituting the π-electron orbitals of the double bond. Twisting of the inter-atomic axis in a bridged-ring system is thus the simplest case of that steric hindrance of π-electron resonance which has recently been much investigated in systems containing several conjugated double bonds. Bredt's rule is formally broken by the products (III) of the Robinson reaction containing a 1 : 3-bicyclic system, and it is therefore clear that a double bond may lie at the bridgehead of a bicyclic system if the ring only be large enough.

We investigated this problem more thoroughly by a variant of Robinson's synthesis.[17] We condensed the cyclanone carboxylic esters with γ-chlorocrotyl chloride (1 : 3-dichlorobut-2-ene) instead of with the quaternary salt of the "Mannich-base" and treated the products (IV) with concentrated sulphuric acid according to O. Wichterle.[18] The γ-chlorocrotyl derivatives give under these conditions γ-keto-butyl derivatives, which react further as in Robinson's synthesis but without saponification and decarboxylation. The carbonyl of the β-keto-carboxylic ester is less reactive than in ketones, and only bicyclic compounds condensed in the 1 : 3 position are formed independently of ring size. The compounds (V) from the starting material with 6- or 7-membered rings contain, however, no αβ-unsaturated carbonyl, as shown by ultra-violet absorption spectra, or in other words they obey Bredt's rule. In contrast, the compounds (VI) with 8-membered and higher ring are αβ-unsaturated ketones. Thus the limit of applicability of Bredt's rule lies between the systems with a 7- and an 8-membered ring.

The bicyclic α-keto-carboxylic acids (V) and (VI), which are obtained by the variant of the Robinson synthesis, show an interesting behaviour on decarboxylation. The compound (V) with two 6-membered rings cannot be decarboxylated even under drastic conditions. Similar examples are known from terpene chemistry, for example, camphoronic acid. On the other hand, the analogous acids, (V) with a 7- and (VI) with an 8-membered ring, decarboxylate easily at 240°, whereas the acid (VI) with a 13-membered ring decarboxylates even during the alkaline saponification of the ester. If we assume that an anion at the bridgehead is an intermediate, which must be stabilised by resonance with the carbonyl for the activation energy to be sufficiently low, then we can use these results as a contribution to the knowledge of the validity of Bredt's rule.

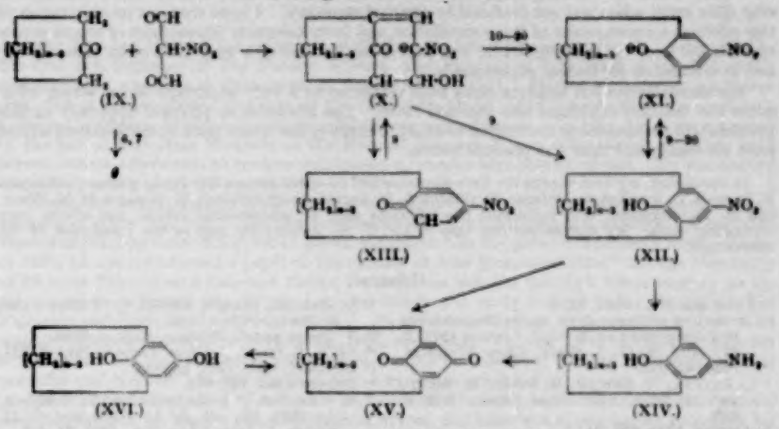
I should like to mention that γ-chlorocrotyl carboxylic esters (IV) can be saponified and simultaneously decarboxylated with a mixture of hydrochloric and acetic acids and that treatment of the resulting α-chlorocrotyl ketones (VIII) with sulphuric acid gives the same products (II) as the Robinson synthesis.

Since all experiments showed that the carbonyl in poly-membered ring compounds is feebly reactive, whereas the α-methylene groups are strongly reactive, we tried to condense cyclic ketones with nitromalonic dialdehyde (IX), which gives substituted *p*-nitrophenols easily with aliphatic ketones as was shown by Hill and by Kenner.[19] In fact, the many-membered ring ketones with a more than 8-membered ring gave compounds of the expected formulæ.[20] However, the influence of ring size on the formation of the bicyclic system showed an interesting effect. With 10- and higher-membered ring ketones yellow *p*-nitrophenoxides (XI) were directly obtained, which yielded on acidification *p*-nitrophenols (XII). Ketones with an 8- and a 9-membered ring gave instead colourless condensation products, which contained one molecule of water more than the expected *p*-nitrophenoxides. These products differ in their absorption spectrum from the *p*-nitrophenoxides and probably have the constitution (X).[21] On acidification, the product with a 9-membered ring gives immediately the corresponding *p*-nitrophenol, which can be converted by alkali into the normal *p*-nitrophenoxide. In contrast to this, the primary condensation product which contains an 8-membered ring gives on acidification a compound (XIII) which is tautomeric with the expected *p*-nitrophenol, as could be shown by a thorough investigation. This compound is converted by alkali back into the colourless salt (X), which contains 1 molecule of water more than the *p*-nitrophenoxide. We have here an interesting case of a compound in which the ring strain has overcome the tendency to form an aromatic system. This is in accordance with the model, which shows that the compound (XIII) is much less strained than the *m*-bridged benzene derivative. The *m*-bridged *p*-nitrophenols can serve as starting material for other series of *m*-bridged benzene derivatives, for example, 4-aminophenols (XIV), *p*-benzoquinones (XV), and quinols (XVI).[22]

In the above mentioned *m*-bridged bicyclic compounds the many-membered rings have forms which are very similar to the forms of monocyclic ketones with "O-inside" constellations: this can be seen from the model of a *m*-bridged *p*-nitrophenol, as shown in Fig. 11. Therefore

it was interesting to test whether the influence of the medium-sized rings on the chemical properties of the bicyclic compounds was the same as in the monocyclic compounds. The

m-Bridged Benzene Derivatives.



aromatic part of the molecule served in these cases as a kind of indicator for the forces inside the ring.

FIG. 12.

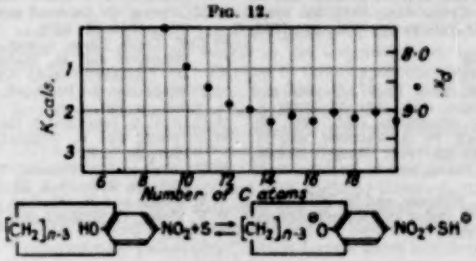
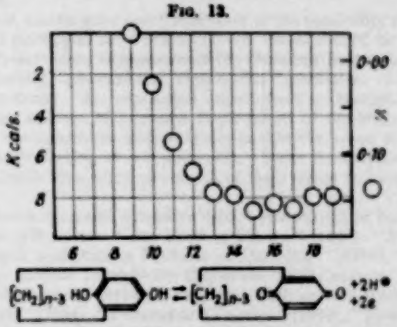


FIG. 13.



We measured the dissociation constants of the *m*-bridged *p*-nitrophenols in 80% Methylcellosolve [31] (cf. Fig. 12) and the redox potential of the *m*-bridged *p*-benzoquinones [32] (cf. Fig. 13).

One can see in both cases that the medium-sized rings stabilise the reaction component with the more nucleophilic oxygen, as would be expected on the assumption of the formation of an intramolecular hydrogen bridge.

I believe that the investigations which we have carried out show clearly that ***a medium-size ring effect exists which was not predicted by classical chemistry.*** I hope that our interpretation of this effect as a consequence of the constellation and intramolecular interactions of atoms across space is not very far from the truth, and that it can be used as a basis for a more exact theory and as a stimulus for further experiments.

The constellation has hitherto often been neglected as a very important factor which influences the reaction equilibria and reaction rates. The advances in physical approach to this problem will perhaps allow the organic chemist to make in the future more valuable contributions from his standpoint than was possible before.

In conclusion, my best thanks for their wholehearted co-operation are due to my younger colleagues P. Barman, L. Frenkiel, O. Häfliger, H. Günthard, W. Ingold, Margrit Kobelt, K. Wiesner, M. M. Wirth, and M. Zimmermann, who performed the laborious and, in experimental details, not always very interesting work. My thanks are due also to Dr. G. W. Kenner for help in the translation of the manuscript.

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OBITUARY NOTICES.

ARTHUR PILLANS LAURIE.

1861—1949.

ARTHUR PILLANS LAURIE, the eldest son of the late Professor Simon Somerville Laurie, LL.D., the first Bell Professor of The Theory, History, and Practice of Education in the University of Edinburgh, was born in Edinburgh on November 6th, 1861. He was educated in his native city, first at the Academy, and then at the University (B.Sc., 1881), proceeding later to King's College, Cambridge, of which he was an exhibitioner and prizeman. In 1884, his name appeared in the list of first class Honours of the Natural Sciences Tripos (Chemistry), together with several others, afterwards to become well known in various branches of science. He was elected into a Fellowship of his College in 1888.

About this period, Laurie made the acquaintance of Holman Hunt, whom as time went on he came to know very well. The Pre-Raphaelite master encouraged him to study the scientific aspects of painting, and thus in effect spread out before him the pattern of his life's work. Then, in 1891, Laurie contributed a paper to the Society of Arts Journal entitled "On the Durability of Pictures Painted with Oils and Resins," which won him the Society's Silver medal; in the same year he delivered the Cantor Lectures before the same Society under the title "The Pigments and Vehicles of the Old Masters." Further contributions to the Society's Journal on cognate subjects appeared in 1892, 1893, 1907, and 1922. To read these in retrospect to-day is to realise that they represent the work of a mind of somewhat unusual character, at once versatile and original. Pathfinder and seer, Laurie has not laboured in vain.

Wide interests continued to dominate his busy life. In 1895, he became Lecturer in physics and chemistry at St. Mary's Hospital Medical School, and later was appointed an Examiner for the Royal College of Physicians, and for the City and Guilds Institute. The Home Office Committee on Pottery Manufacture also claimed him as a member. Always interested in educational matters, he was Assistant Commissioner to the Royal Commission on Secondary Education in 1895, and in 1900 accepted the Principalship of the Heriot-Watt College in his native capital. Twelve years later, he added to his responsibilities the Professorship of Chemistry in the Royal Academy of Arts. The first of these appointments he held for 28 years, and the second for 24 years. Meanwhile, in 1895, he had obtained the degree of D.Sc. (Edinburgh), for a thesis entitled "The Constitution of Alloys."

The war of 1914—18 found Laurie in constant request, largely on account of his acquaintance with the late Earl Lloyd George who appreciated the value of his capacity for swift experimentation and breadth of technical experience. He served on numerous Bodies connected with supply and inventions, as well as being concerned with Building Research, to which reference is made later. Running through all these activities can be perceived the influence of a sound "classical chemistry;" his training and outlook supplied the basis for what an earlier generation would have called "experimental philosophy," which Laurie knew instinctively how to apply to the problems at issue.

Between the two wars, Laurie gave much attention to the possibility of using ethyl silicates as stone preservatives; in particular his work on silicon esters should be mentioned. He was a member of the Stone Preservation Committee of the Building Research Board, and then, from 1926—1930, of its Standing Chemical and Weathering Committee. Earlier he had published several papers on stone decay. He conducted experiments at Hampton Court and elsewhere in collaboration with the Ancient Monuments Department of the Ministry (then the Office) of works. In favourable circumstances silicon esters enable the stone to be hardened and consolidated without the introduction of a soluble salt. Later developments have been in other directions, but it is probable that they owe much of their value to Laurie's pioneer interest in ethyl silicates.

Laurie's published work covers an extensive field. His output of books alone is impressive, as the following resume will show—"The Food of Plants" (1893), "Processes, Pigments and Vehicles" (1895), "Greek and Roman Methods of Painting" (1910), "Materials used in the Painter's Craft from the Earliest Times to the End of the XVII Century" (1911), "The Pigments and Mediums of the Old Masters" (1914), "Painters' Methods and Materials" (1926), "Simple Rules for Painting in Oils" (1934), "Pictures and Politics" (1934), "New Light on Old Masters" (1935), and "The Technique of the Old Masters" (1949).

In addition to these volumes, several of them of considerable size and scope, Laurie

contributed on various occasions to the usual scientific periodicals. He became interested in the way in which the refractive index of paint media in pictures might serve as an indication of the picture's age. (It is, of course, well known that the medium becomes progressively more transparent with the passage of time; it is this effect which is mainly responsible for the appearance of *pentimenti*.) In 1937 he discussed the sorption of organic liquids by raw linseed oil and stand oil films, and the anomalous results to which it gave rise in the study of the refractive index of such films.

Less known in this country are the articles which Laurie wrote for "Technical Studies in the Field of the Fine Arts" (1933—1942), issued by the Fogg Art Museum, University of Harvard, U.S.A. The following is a complete list, in chronological order:

The Use of an Emulsion as a Painting Medium	1933
Examination of the Masks of Mummified Bulls	1934
Notes on the Medium of Flemish Painters	1934
Materials in Persian Miniatures	1935
Problems connected with the Cleaning and Preservation of Pictures	1935
The Microscopic Examination of the Surface of a Picture	1935
Restrainers and Solvents used in Cleaning Old Varnish from Pictures	1935
The Yellowing of Linseed Oil	1936
The Fayum Portraits Painted in Wax	1937

"Auld Reikie" contributed her garlands as the years went on, the Royal Society of Edinburgh its fellowship in 1885, and the University the honorary degree of LL.D. in 1929. Laurie also became an Honorary Royal Scottish Academician.

He died at Haslemere, Surrey, on October 7th, 1949, and is survived by his only daughter, who shared his life and interests through many years.

He was elected a Fellow of the Chemical Society in 1886.

F. I. G. Rawlins.

SIR HENRY MIERS.

1858—1942.

Few Fellows of the Chemical Society can have had a more active, a more varied, and a more useful life than Henry Miers. Save for failing eyesight he never grew old, and for nearly sixty years his alert, tireless, keen, smiling little figure was never idle, ever ready with help and advice, whether it was in the British Museum, Oxford, London, or Manchester. He had many interests, but it was his interest in human beings, his genius for helping others to shape their lives, that so many of us remember with gratitude. Perhaps that is not surprising in the great-grandson of Francis Place, one of the great social reformers of the early nineteenth century, the joint founder of University College, London, and a pioneer in adult education. Miers was proud of his ancestry. His father was a distinguished civil engineer, his grandfather, also an engineer, had travelled widely in South America and in 1843 was elected to the Royal Society for his botanical studies. Miers had an elder brother, Edward John Miers, who was a zoologist on the staff of the British Museum. So science and education were in his blood.

He was born at Rio de Janeiro on 25th May, 1858, and two years later his father retired from his South American business and settled in South London. Miers' preparatory school was Summerfields, just outside Oxford, where that skilful teacher Mrs. Maclaren gave him a taste for classics which lasted all his life. In 1872, like so many of his schoolfellows, he won an Eton scholarship. In his five years at Eton he remained true to classics, eventually winning a classical scholarship at Trinity College, Oxford. However his interests were widening in mathematics and science, and on going up to Oxford in October 1877 he read for both Classical and Mathematical Moderations. He had intended to take both the Honours Schools of Mathematics and Physics, but he was getting interested in crystallography, and hearing that there would soon be a vacancy in the Mineralogical Department of the British Museum he decided to throw up his Science School and devote himself entirely to the competition for that post.

Story Maskelyne was then Professor of Mineralogy in Oxford, but he was also a Member of Parliament living in London; he had no Department and lectured only when required. Miers was his only pupil, but Maskelyne came up each weekend to lecture to him, though the lectures soon degenerated into armchair discussions at the home of the witty Professor of Geometry, Henry Smith, who took a lively part in the talks. What could have been more stimulating for a young and enthusiastic undergraduate?

After taking the Final School of Mathematics, Miers went for three months in 1882 to work in Strasbourg with Groth, with whom he formed a lifelong friendship. The work for his first published paper on cerussite was done during the visit. After all this careful preparation Miers came out top in the Civil Service examination, the only serious competitor being Sanderson, the future headmaster of Oundle.

In October 1882 Miers entered on his new duties at a fortunate moment. The mineral collection had just been moved from Bloomsbury to its fine new quarters in South Kensington, and the new Head of the Department, Lazarus Fletcher, was a kindred spirit who appreciated the fine qualities of his new assistant. Miers helped in the rearrangement of the collection, but he had ample time for research and he took full advantage of the material available for investigation. He remained at the Museum till 1895, and during those years he contributed a long series of papers on the morphology of various crystal species. By them he proved himself an accurate, painstaking investigator, with a quick eye for any abnormality of habit and for points of special crystallographic interest. His most important work was with G. T. Prior on the red-silver minerals, in which they cleared up the relationship of pyrargyrite, xanthoconite, and rittingerite and discovered a new species which was named sanguinite. Although his problems were mainly crystallographic, Miers quickly became a first-class mineralogist. Minerals appealed to his aesthetic taste, he had a wide knowledge of their occurrences and associations, and he was never happier than on mineralogical excursions in Cornwall and elsewhere.

However in spite of the opportunities for research the life of an assistant at the Museum did not for long satisfy the humanism of one who had such a variety of cultural interests. He always longed to be a teacher, and, at the invitation of Arthur Hugh Clough, he gave evening lectures on experimental science, at a neighbouring Board School, to elementary school children. In 1886 his real chance came when H. E. Armstrong, by a stroke of genius, asked him to teach Crystallography in the City & Guilds Technical College. He worked there after Museum hours, and soon built up a small Crystallographic Department which, with the exception of Cambridge, was the first of its kind in this country. Miers' most distinguished pupil was W. J. (afterwards Sir William) Pope, who succeeded him as lecturer in 1895. Pope's first paper was published jointly with Miers, and his early interest in crystals coloured much of his subsequent research.

Miers' energy found many other outlets—foreign travel, visits to most of the great continental mineral collections, and collaboration in a book on "The Soil in Relation to Health," the result of his intimacy with a number of young doctors. His interest in ballooning nearly cost him his life. An aeronaut named Simmons had advertised a balloon flight to Austria, and offered to take one or two passengers. Miers got a few days' leave from the Museum and without telling anyone where he was going he flew off from the Danish Exhibition with Simmons in his large new balloon; the other passenger was a young man named Field. As the wind was from an unsuitable direction Simmons decided to descend for the night near the coast. A strong wind was blowing, and while anchored to a tree near Maldon the whole balloon blew to pieces, and the wire basket with the occupants fell sixty feet to the ground. Simmons was killed, Field broke both legs, Miers was picked up unconscious, and it was six weeks before he could go back to work.

In 1895 came the most spectacular event in his scientific career. He was at the meeting in Burlington House when Ramsay announced the discovery of argon by Lord Rayleigh and himself. The same night Miers wrote to Ramsay suggesting that he should examine the gas given off when cleveite is heated with dilute sulphuric acid, which Hildebrand had thought to be nitrogen. He told Ramsay where he could get the mineral, and six weeks later Ramsay sent the gas from cleveite to Crookes, thinking it might be krypton for which he was looking. Crookes telegraphed back "Crypton is helium. Come and see it." Towards the end of his life an old friend was congratulating Miers on his long innings, saying that in giving the clue to the discovery of helium he hit the ball over the pavilion. Miers replied with characteristic modesty "Oh no! The helium episode was only a timid but lucky swipe which happened to sneak through to the boundary."

Later in the year Miers was appointed to the Waynflete Professorship of Mineralogy at Oxford in succession to his friend and teacher Story Maskelyne, and in 1896 he was elected a Fellow of the Royal Society. He was delighted to return to Oxford, where he had spent four happy years as an undergraduate, with the prospect of creating a research school of Mineralogy, and with long vacations for foreign travel. The Professorship carried with it a Fellowship of Magdalen, and for thirteen years he gathered round him an ever-widening circle of friends, whom he loved to entertain in his rooms in the New Buildings overlooking the Deer Park.

The rooms in the Museum assigned to the Professor were quickly converted into small but well equipped laboratories for teaching and research, and it was not long before Miers had a

small group of keen students. He was an admirable lecturer, and however small the audience Miers gave of his best. Clear and simple, stimulating and full of interest, each lecture was a well-rounded exposition of some topic, which sent us away feeling that for the moment at any rate we understood. I remember as a schoolboy the thrill of hearing his Cantor Lectures on Gem Stones.

Everyone who came under his influence was attracted by his personal interest in them and the happy gift he had of suggesting some subject for research that was within their competence. Among his students were Herbert Smith, who went to the British Museum, H. L. Bowman, who succeeded him in his Chair, T. V. Barker, whose untimely death was a great loss to crystallography, Jacques Chevalier, later Professor of Philosophy at Grenoble, Noel Ashcroft, afterwards President of the Mineralogical Society, and his two assistants R. C. Spiller, now Reader in Mineralogy at Oxford, and R. P. D. Graham, now Assistant Professor of Mineralogy at McGill, who writes of him :

" He was a man of great kindliness, possessed of infinite patience and a disposition that refused to be ruffled. In all the years I was associated with him, I do not recall a single occasion on which he complained, or was impatient, or expressed displeasure when things went wrong or mistakes were made, which doubtless was often enough. Instead, there was always an explanation of the cause of the trouble and instruction as to how it might be avoided in future. These characteristics, and a genuinely personal interest in his students, explain his success as a teacher, for, in his lectures, each individual was made to feel that it was he, personally, who was being addressed. His " Mineralogy," first published in 1902, well illustrates his lucid and systematic method of teaching. It unquestionably set a new standard for textbooks of mineralogy and crystallography. Several that have been published since that time are quite obviously modelled on Miers, and one or two may even be said to mirror it, though in much distorted fashion. But in nearly forty years of teaching experience, the writer has failed to meet with a better ' Introduction to Mineralogy ' than that given us by Miers."

Miers' most important work at Oxford had its origin in his earlier crystallographic papers when his accurate measurements so often showed the existence of differences in interfacial angles even on the same crystal which were much larger than the errors of observation. Previous attempts to elucidate the problem of these " vicinal " faces by elaborate series of measurements on mineral crystals had been unproductive, and Miers decided that the most helpful method of attack was to measure the angles of crystals actually growing in solution. For this purpose an inverted goniometer was built by Troughton & Sims with which the angles of growing crystals could be measured, including the small angles between a group of vicinal faces by means of a new form of micrometer eyepiece. Most of the work was done with cubic crystals (the alums and sodium chlorate) as there was then no doubt as to the theoretical values of the interfacial angles. The experiments showed that crystal growth under these conditions takes place on groups of vicinal faces inclined at small angles ranging from 3′ to 20′ to the cubic or octahedral face under examination. A few crystals belonging to other systems were examined and the same phenomenon was found. During the growth of a crystal sudden changes occurred in the inclination of the vicinal faces. These changes always occurred *per saltum* and not continuously, showing that new plane crystal face had come into existence, and that growth did not give rise to curved faces. There were indications that the inclinations to the normal face increased with increasing concentration, but the experiments were not definite on this point.

The results thus justified Miers' intuition that the study of growing crystals was the best way of advancing our knowledge of vicinal faces, as, without knowledge of the whole history of the growth of a crystal, measurement of its final condition might lead to quite erroneous conclusions.

Miers pointed out that the vicinal faces correspond to a much more open packing of the molecules than the normal faces, and that as the molecules are much more densely packed in the crystal than in the solution (45 times in the case of alum solution) it might be easier for the molecules to be deposited in the more open layers. Miers' paper was a most enlightening contribution to a problem that had puzzled generations of crystallographers, and one wishes that he had pursued it further and by growing crystals under carefully controlled conditions had investigated the factors that cause the variations in the vicinal faces. His attempts were, however, diverted to another aspect of crystal growth. He determined the concentration of the solution in contact with the growing face by using the crystal as a prism to measure the refractive index of the solution. This involved the determination of the effects of temperature and concentration on the refractive index of the solution. In the course of the measurements Miers and Miss Florence Isaac, who joined him in the investigation at this stage, found that the refractive

index of a cooling solution increased rapidly until a few crystals began to form, and that at a later stage the refractive index fell rapidly as a cloud of crystals was suddenly produced. I found them one day in the laboratory rather puzzled by this, and suggested that these effects might be due to the transition of the supersaturated solution from the metastable to the labile state as predicted by Ostwald. Trials made by cooling aqueous solutions in sealed tubes showed that crystallisation did not occur spontaneously until a considerable degree of supersaturation was reached, the metastable region being represented by the area between the solubility curve and the curve which Miers named the supersolubility curve, showing the concentrations at which spontaneous crystallisations take place.

Together with Miss Isaac, he undertook a number of investigations of the conditions under which spontaneous crystallisation occurred both in aqueous solutions and also in mixtures, as he thought this was of importance in throwing light on the crystallisation of igneous magmas. With Jacques Chevalier too he investigated the differences in the growth of crystals in the metastable and labile regions.

Another outcome of this work was Miers' interest in the effect of one species in affecting the deposition of others which led to the comprehensive study by T. V. Barker of parallel overgrowths resulting in the discovery of a number of interesting relationships.

Miers made full use of the Long Vacation for foreign travel. Visits to the United States and Canada, and then to Russia to learn the language, were followed by an adventurous trip to Klondyke in 1901 at the invitation of the Canadian Government. In 1903 he went to South Africa at the invitation of the Rhodes Trustees to look into educational problems, and again two years later for the British Association meeting at Johannesburg, when he was President of the Geological Section.

Oxford soon discovered in Miers a most valuable recruit for University business. His equanimity, wide interests, and readiness to help, and his untiring energy were a great asset to the University. As Secretary to the Museum Delegates he took a very active part in the administration of the Museum. Most of the stone capitals had been carved by the brothers O'Shea under Ruskin's supervision, but some were still unfinished. Miers found a benefactor with whose help the remainder were carved with floral designs following the original tradition. He served as a delegate of the University Press, a member of the Hebdomadal Council, and as Junior Dean and Vice-President of Magdalen, while at the same time he had many duties in London as Editor of the *Mineralogical Magazine*, President of the Mineralogical Society, and Vice-President of the Chemical and Geological Societies.

It was Miers' constant touch with the outside world that made him a particularly valuable member of the University. But as a result his reputation as an administrator got abroad, and in 1908 he was invited to succeed Sir Arthur Rücker as Vice-Chancellor of London University. Miers felt it was his duty to go although he hated giving up his teaching and research. He had often said that he wished to make way for younger men and was afraid of the stagnation of advancing years in Oxford.

He went to London at a difficult moment. The University was divided and unsettled by the strong antagonisms between the external and internal parties, which were intensified by the fact that Lord Haldane's Royal Commission on the University was sitting and taking evidence. Miers' time was largely taken up by meetings of Councils and Committees. He was a member of the Governing Bodies of all the constituent Colleges, and there were innumerable problems to be faced. Miers had very happy relations with Lord Rosebery, the Chancellor of the University, and his unbiassed Chairmanship of the Senate was a great help at a difficult period. In 1912, the year he was knighted, Miers, against considerable opposition, persuaded the Universities of Great Britain to hold a Congress of the Universities of the Empire in London. This led to the foundation of the Universities Bureau and to future quinquennial meetings of the Congress.

In London Miers missed more and more the close personal relations with students, and when the war came he saw that the recommendations of the Haldane Commission might not be implemented for many years. So in 1915 he accepted an invitation to go to Manchester as Vice-Chancellor, as he felt he might be more useful in a smaller University, particularly as he was also to be Professor of Crystallography and to do some active teaching.

It was a successful experiment, and Miers spent eleven very happy years in Manchester. His modesty, his friendliness, his range of interests, and his charm as a guest or host quickly won the hearts of the Lancastrians. He threw himself into their problems, not only at the University but in the intellectual life of the community, and he did a great work in bringing the City and the University much closer together. He became the social focus of the University, and he gave

both to its graduate and undergraduate life a more closely knit personal structure, which is much more difficult to achieve in " Red Brick " than in one of the older residential universities.

It was not an easy time for a Vice-Chancellor. First he had the war problems, and then the period of reconstruction. But under Miers' care the University gathered strength, and his Vice-Chancellorship was marked by many new developments. Under his sympathetic guidance the University took its full share in civic activities.

He was particularly happy once again to be Professor of Crystallography. He lectured regularly with his old skill, and whenever he could snatch an hour from official duties he was in the laboratory helping the students with that encouragement and personal interest that so many of them remember with affection. He was too busy to do any research himself, but he took the keenest interest in the work that was in progress, very happy that it was in his own field, the effect of environment on crystal growth.

His term of office would normally have ended in 1923, but the Senate pressed him to remain until 1926. When he left he must have been touched by the warmth and spontaneity of the many tributes from the University and the City for all that he had done for them.

In 1926 he returned to London and bought a house in Hampstead, meaning to return to his scientific work. But it was not to be. First there were jobs to be rounded off, and then, ever willing and eager to help in any constructive work, he was drawn into fresh activities.

In 1926 he undertook a Report on our Museums and Art Galleries for the Carnegie United Kingdom Trustees with S. F. Markham as his Secretary. As a result Museums became his chief occupation and interest for the rest of his active life. He served on the Royal Commission on Museums and on the Standing Committee appointed to carry on its work. He was President of the Museums Association for six years and with Markham he made a survey of the Museums in the Empire for the Carnegie Corporation. Miers was convinced of the great part Museums could be made to play in the life of the people if they were recast and for ten years he was the acknowledged centre of progress in all museum work.

As the years wore on, even his tireless energy began to flag, and when his eyesight failed and made travelling difficult the Museum work was left more and more to Markham. But he was never idle, and in these last years his happiness was the collection of plants in the London district and the care of his collection of photographs of classical sculpture. He never lost his enthusiasms and his interest in the doings of friends and pupils.

Miers's life was spent in the service of others. He was a fine teacher of the most generous type, clear and encouraging, and making everyone feel that there was a place for him in the world. Modest, unselfish, loving his fellow men, he was perhaps a little too gentle at moments in debate when a firm lead was needed. But he was a great humanist, and at times like these when the ethical influence of science is often called in question, Miers is an example of what a man of science can do in applying scientific methods in administration, and to the wider problems of academic and national life.

HAROLD HARTLEY.

SIR ROBERT ROBERTSON.

1869—1949.

THE death of Sir Robert Robertson at the age of eighty removes from our midst a man of outstanding personality. Primarily an expert of world-wide repute in the field of explosives, he had a great variety of other interests, mainly scientific, but including also such subjects as classics and historical research. He was a Fellow of the Chemical Society for over forty years and was twice a Vice-President.

Robert Robertson was born on April 17th, 1869, in Cupar Fife, and was the son of J. A. Robertson, D.D.S. Both the father and the grandfather had somewhat of a scientific bent. Robert was the eldest of a family of four; of his three sisters one, Jess Isabel, married William Rintoul, a colleague of Robertson's in his explosive work. Robertson was married in 1903 to Kathleen Stannus, daughter of Hugh Stannus, F.R.I.B.A., lecturer in Applied Art at South Kensington and Manchester. She inherited his artistic ability and has produced many charming works of art. She died in 1938. Two children, a daughter and a son, survive Sir Robert.

1876—1885.

At the age of seven Robertson entered the Madras Academy, Cupar Fife. The curriculum did not include science, but a small laboratory was fitted up at home. He showed great

industry at school and gained many prizes. On leaving, he was awarded the Balgonie Gold Medal. In the Senior Local Examination of St. Andrews University he was placed first in Scotland and won the University prize.

1885—1890.

Robertson matriculated at St. Andrews University in October 1885 for the M.A. degree. In the 1885—1886 Session there were sixty "bejant" students, as they are called at St. Andrews in their first academic year. Two of these, Robert Robertson and Alexander MacKenzie, attained the distinction of the Fellowship of the Royal Society.

The course extended over four Sessions. No chemistry classes were included; it was, however, possible to take extra classes if time permitted and Robertson found that he could attend classes in science in his third and fourth years, which would enable him to qualify for the B.Sc. degree. A fellow student, David Lawson, who had attended Purdie's chemistry lectures, spoke enthusiastically to Robertson about them and he decided to enter for a chemistry class. In the following year he took a more advanced class and came for the first time under the stimulating influence of Purdie. This made a tremendous impression on him and ultimately a life-long friendship sprang up. Robertson took the M.A. degree in 1889, and in 1890, after a further summer course, he took his B.Sc. degree.

His affection for his old University was almost a passion. In his later life he was a founder member of the St. Andrews Club, London (1904), and was for many years Chairman of Council. He was always interested in historical studies and made a study of the Avignon Popes of whom the last, Peter de Luna (Benedict XIII), founded St. Andrews University in 1411.

1890—1892.

On leaving College, Robertson entered the laboratory of the City Analyst in Glasgow and worked under Robert T. Thomson (who recently completed his fiftieth year as a Fellow of the Chemical Society). Through him, Robertson made the acquaintance of James Miln Thomson, manager of the Cordite Section of the Royal Gunpowder Factory at Waltham Abbey, and this was destined to lead his steps into the explosives world.

1892—1907.

In 1892 Robertson was appointed as a junior chemist (at twenty-seven shillings a week) under J. M. Thomson. Thomson encouraged his young assistants to undertake investigations, to give them a greater interest in their work. He set Robertson to work on the relationship between the nitrogen content of nitrocellulose and its solubility in ether–alcohol. Robertson also made experiments on the preparation and properties of ethylene dinitrate, and on the basis of this work he obtained the D.Sc. degree of St. Andrews University in 1897.

A further practice, instituted by J. M. Thomson, was that his young chemists should spend six months learning factory operations side by side with the workmen; thus Robertson acquired a first-hand knowledge of the processes.

In 1894 there was a serious explosion in the nitroglycerine plant. With great pluck Robertson and two others "drowned" the remaining nitroglycerine in water and thus probably averted a further explosion. For this act he was presented with a gold watch by the Government. He regarded this watch as one of his most valued possessions. He was placed in charge of the nitroglycerine manufacture until 1900. During this time he and William Rintoul worked out a process for recovering acetone vapour, which had previously been allowed to go to waste in the cordite driers. This depended on absorption by sodium hydrogen sulphite and was applied on a very large scale.

In 1900 Robertson was put in charge of the Main Laboratory. He had a certain amount of time available for research and made a study of the Will stability test for nitrocellulose in its application to the purification of gun-cotton by boiling with water. He found that the best method of purification was to boil the gun-cotton initially with weak acid to hydrolyse unstable impurities; the acids could then be removed by prolonged boiling with water. This valuable discovery was published in 1906 and has become the standard practice in gun-cotton manufacture. He followed up this work by modifying the Will test to adapt it to the measurement of the rate of decomposition of nitroglycerine.

In a further research with S. S. Napper the absorption spectrum of nitrogen dioxide was examined and it was found that nitrogen dioxide could be detected and measured in low concentrations in air. This was utilised to measure the gradual decomposition of nitrocellulose at medium temperatures.

At about this time some of the cordite came under suspicion of having inflamed spontaneously. The Will test threw no light on this, and Robertson introduced a new stability test, the "Silvered Vessel Test." The cordite was ground and heated at 80° in a vacuum-jacketed and silvered flask. The decomposition was detected, first by visible fumes of nitrogen dioxide and then by a rise of temperature. The cordite then in use contained 5% of mineral jelly, and he found that if the mineral jelly were omitted or replaced by saturated hydrocarbons the stability was greatly decreased. From this it was deduced that mineral jelly contained a small proportion of hydrocarbons which reacted with nitrogen dioxide. Since nitrogen dioxide acts as an auto-catalyst in the decomposition its removal is beneficial to the stability.

A field of work which was the subject of considerable investigation by Robertson was the calorimetry of the explosion of cordite. This was based on the work of Sir Andrew Noble. The cordite was placed in a thick-walled steel bomb which was immersed in a calorimeter. The effect of mineral jelly and of the proportion of nitroglycerine was measured.

1906—1907.

In the summer of 1906 spontaneous explosions took place in two magazines in India. This required urgent investigation, and Colonel Nathan and Dr. Robertson were sent out to India to undertake this. The Silvered Vessel Test proved its value in correlating the decline of stability with the temperature and time of storage, and it was possible to lay down a safety limit, below which the test should not be allowed to fall. An exhaustive report was made on the conditions of storage with recommendations for the preservation of cordite in hot climates, and this remained for many years a classic source of reference.

1907—1914.

On his return from India early in 1907, Robertson was invited to take up the position of Superintending Chemist at the Woolwich Research Department. This Department had been in existence for about six years. It arose out of an experimental establishment set up by the Explosives Committee. The Committee included a number of illustrious scientists, among whom were Lord Rayleigh, Sir William Crookes, and Sir Andrew Noble. They took a personal interest in the work, which was very encouraging to the small staff of about half-a-dozen chemists. The original terms of reference were to improve the detonation of lyddite and to overcome the defects of the cordite at that time in use. The work, however, widened rapidly; many explosives were synthesised and examined, notably trinitrophenylmethylnitramine, for which a manufacturing process was worked out. Important work on the stability of propellants was carried out and the study of trinitrotoluene was commenced. New and well-equipped laboratories were built and the work expanded greatly. Unfortunately, the scientific Explosives Committee gave place in 1906 to a Board in which science had relatively little representation and in 1907 a military "Superintendent of Research" was appointed. Such was the background of the Department at the time of Robertson's appointment on April 7th, 1907. His University course for the M.A. degree had left him relatively little time to obtain a comprehensive knowledge of chemistry, but he brought a valuable fund of technical experience and a useful knowledge of safety precautions to the Department. His organising ability had full scope; he was a good administrator and had abundant energy; painstaking, methodical, and cautious in arriving at decisions, but obstinate in adhering to them in the face of any opposition. He was domineering and issued his instructions in the form of abrupt and peremptory orders. The junior members of the staff were terrified of him.

He realised the necessity of amassing a systematic fund of information on all subjects connected with explosives. This aided in dealing with the increasing influx of Service problems.

In view of its importance the stability of cordite was one of the most prominent subjects of investigation. The deterioration of cordite starts from minute nuclei of impurities and spreads by autocatalysis. An exhaustive study of the nature of the harmful impurities was made by means of climatic storage trials. This led to a better control of the cordite stored in magazines and to the introduction of precautions in the manufacture.

Work on high explosives was also in progress. A comprehensive study of the properties of trinitrotoluene was made and the manufacture and purification of trinitrophenylmethylnitramine were perfected. Important researches on the initiation of detonation of high explosives and the sensitiveness of explosives to impact were carried out. Robertson showed a keen interest in the progress of the work; he also fulfilled a useful function in establishing contacts with

other Service departments. The opportunities for publication were very restricted on account of its secrecy.

1914—1918.

With the outbreak of war in August 1914 the Research Department was put to a strenuous test. With a staff of nine chemists and subordinate staff it was required to cope with a host of problems in a minimum of time. The work was so wide-spread that it cannot be dealt with in any detail. A few outstanding examples may, however, be mentioned.

In October 1914 improvement in the supply of trinitrotoluene (T.N.T.) became extremely urgent. Robertson was asked whether his Department could make three tons a week of T.N.T. to relieve the position. He immediately gave orders that work should be put in hand at the highest pressure to establish the most efficient method of manufacture. The existing processes were slow and inefficient. They also required oleum, which was not available. Intensive laboratory work was put in hand and a number of radical improvements were worked out. After a short time the work had reached a stage at which an experimental plant could be designed. Robertson's technical knowledge then stood him in good stead; he made a personal search of the scrap heaps of Woolwich Arsenal to find the necessary equipment and a plant for three tons a week was soon erected. This gave successful results and it was kept in production for a considerable time. In the early stages the supply position was so crucial that each week's output was seized upon with avidity for shell-filling, etc. This process was taken as the basis of the design of the large-scale Government plant at Oldbury and later that at Queensferry.

Although this work led to the expansion of T.N.T. production to a very large scale, it was still limited by the available toluene and it soon became evident that a still larger supply of high explosive would be required. In order to eke out the T.N.T. the use of a mixture of T.N.T. and ammonium nitrate was investigated at the Research Department. Trinitrotoluene is in itself deficient in oxygen whilst ammonium nitrate has a slight excess. A balanced mixture would be obtained by adding about four parts of ammonium nitrate to one part of T.N.T. At that time it was necessary to add about 40% of T.N.T. to enable the mixture to be melted to a slurry and poured into shells, but this was remedied later and made it possible to use the mixture containing 80% of nitrate. The detonation of this mixture was a difficult matter and numerous other difficulties arose such as hygroscopicity, corrosion of metals owing to hydrolytic dissociation, formation of dangerous salts with copper, etc., decomposition of T.N.T. by traces of pyridine and thiocyanate, transitions of crystalline form at −16°, 32°, 85°, and 125°. The ammonium nitrate had to be made from Chile saltpetre by double decomposition and was difficult to purify. These difficulties were overcome step by step and this " dilution " of the T.N.T. enabled the quantity of available high explosive to be increased enormously. The mixed explosive was named " Amatol." (I have refrained from mentioning names of the staff working under Robertson, but think that the name of E. R. Deacon, who has since passed away, should be put on record for his valuable work on amatol.)

Another difficulty was that amatol gave little or no smoke on detonation and this made it difficult to locate the burst of the shell. To remedy this, smoke mixtures were devised and incorporated into the shell filling.

Meanwhile serious difficulties arose in the production of cordite owing to shortage of acetone. It was necessary to devise a propellant of the same ballistic properties as cordite M.D. without using acetone; it was also necessary that manufacture should be capable of being carried out in the existing plant. This was met by the introduction of a new propellant, " Cordite R.D.B.", in which the solvent used was a mixture of ether and alcohol. This propellant was ultimately manufactured in enormous quantities in the largest propellant factory at Gretna.

As the war proceeded, the difficulty of obtaining chemists for research work and for manning the factories became more and more acute. Scientists had been sent to the Front regardless of their value in producing vital supplies of munitions. It is amusing to read in a leaflet issued by the Parliamentary Recruiting Committee the advice given for Enlistment in Special Corps : " Men specially enlisted (a) such as Navvies, Tunnellers and Chemists."

In 1917 Robertson went to France and interviewed many scientists. This ultimately led to the return of valuable scientific workers to this country.

At the end of the war in 1918 the staff of scientists numbered one hundred and ten. When the news of the Armistice arrived, Robertson and a group of the staff were engaged in a conclave. It was typical of Robertson that he solemnly proceeded with the discussion and for another hour the scientists had to possess themselves in patience and continue the discussion.

During the war Robertson worked untiringly. He made a point of visiting the laboratories

as often as possible to get first-hand information on the progress of the work. I think it may be said that this formed the peak of his long and active career. He was in the prime of life and rendered truly great services.

It was during the first World War that he was elected a Fellow of the Royal Society (1917). In 1918 he was created a K.B.E. in recognition of his valuable work.

1919—1921.

Much research work remained to be done after the war, but the staff dwindled rapidly after the Armistice. Robertson's time was very much occupied in the question of reorganisation of the conditions of employment of scientists. He continued to be a member of the Ordnance Committee and several other Committees until he left the Department on March 6th, 1921.

1921—1936.

On the retirement of Sir James Dobbie, F.R.S., from the post of Government Chemist, Sir Robert was appointed to this position and took up his duties on March 7th, 1921. In the Government Laboratory, which was already very efficiently organised, he was free to devote himself to work which was congenial to him. He took part in many committees and found time for private research.

The post of Government Chemist carries with it other duties, as he is Chief Agricultural Analyst, Referee under the Food and Drugs Act, and Advisor to the Board of Customs and Excise. The magnitude of the work of the Government Laboratory can be judged to some extent from the impressive Annual Reports. It increased largely during Sir Robert's tenure, owing to legislation such as the Safeguarding of Industries Act, etc.

Apart from the routine analytical work, special investigations were carried out at the Laboratory to assist Departments of State, *e.g.*, the carriage of dangerous goods at sea, the elimination of sulphur dioxide and nitrous gases in the atmosphere, the effect of lead tetraethyl in petrol on health, the investigation of the mineral resources of the Dead Sea for the recovery of potassium chloride, bromine, etc. Sir Robert served on numerous Committees dealing with these and other subjects.

Research on Infra-red Absorption Spectra.—Robertson's great wish was to devote himself to research. He told me that he felt he must do research "to save his soul." The work on infra-red spectra dealt with the three hydrides NH_3, PH_3, AsH_3. Robertson's interest in the subject arose out of the explosive nature of arsine gas, and the original object was to determine whether its decomposition would be accelerated by exciting the molecule with one of its vibrational frequencies. He was fortunate in having the collaboration of J. J. Fox, who had considerable experience in spectroscopy. The work was described in a series of papers in the *Proceedings of the Royal Society* by Robertson, Fox, and Hiscocks.

Special precautions were necessary to overcome the effects of electro-magnetic disturbances and mechanical vibrations caused by heavy road traffic. A tetrahedral structure was deduced for each of the three molecules, though not of equal height. The moments of inertia were calculated. In addition to the rotation system shown by PH_3 and AsH_3, NH_3 was found to have a further system of rotation. Beer's law was found to hold accurately. At that time there were very few infra-red spectrometers in the whole world. There is no doubt that the work of Robertson and his colleagues greatly stimulated infra-red spectrometric work in this country and abroad.

Research on Diamonds.—The published work on the infra-red spectrum of diamonds showed some discrepancies and Robertson proceeded to make a study of diamonds from different sources. In the examination of the first six diamonds one behaved abnormally. The other five gave a strong absorption band at 8 μ, but the sixth gave no such band. Later, other examples of this abnormality were found. Differences were also found in the ultra-violet. Other physical properties were examined; some of these properties showed differences between the normal diamonds (Type I) and the abnormal (Type II). In all, six abnormal diamonds were found, out of a total of three hundred examined. The joint work (Robertson and Martin) was summarised in the Jubilee Lecture to the Society of Chemical Industry (*Chem. and Ind.*, 1944, 18) in which the significance of the physical properties was discussed and surmises were made as to the conditions of formation of the two types in Nature.

Robertson took some interest in the question of the artificial production of diamonds and examined the minute specimens left by J. B. Hannay to the British Museum in 1880. At least one of these proved to be of the abnormal type.

1936—1939.

Robertson retired from the Government Laboratory on April 16th, 1936. He continued, however, to serve on several Committees. In 1937 he resumed experimental work at the Davy Faraday Laboratory. He designed and made apparatus for the exploration of spectra into the deep infra-red, *i.e.*, from 100 μ. downwards. In the middle of 1939 the war clouds became ominous and at the age of 70 he offered his services to his old Research Department at Woolwich.

1939—1945.

At the outbreak of the war, the work of the Research Department was decentralised. Robertson was placed in charge of the section which was stationed at University College, Swansea. The work was already well organised and Sir Robert was thus free to spend a large proportion of his time on Committee work under the Scientific Advisory Council, where his wide knowledge of explosives was of great assistance. In 1939 he was appointed Chairman of the Committee on Higher Explosives. From 1940 to 1942 he was Chairman of the S.A.C. Committee on Chemistry of Explosives and Physics of Explosives. He served also on a number of other Committees. The attendance at the meetings in London involved a great deal of travelling and included some hundred night journeys, an effort which would have taxed the strength of many a younger man. He was awarded the Davy Medal of the Royal Society in 1944 in recognition of his valuable services to Science and the Nation.

1945—1949.

At the end of the war Robertson had attained the age of 76, but was still full of vigour. He resumed his work at the Davy Faraday Laboratory, perfecting the technique of infra-red work and experimenting on the synthesis of diamonds. He extended Hannay's work and endeavoured to obtain crystalline carbon from solutions of cyanides in molten silver and other metals.

He was a member of the Armaments Research Advisory Board until his death. He was Chairman of the Committee which dealt with the Armstrong Memorial Fund (1945—1948). He continued as a Censor of the Royal Institute of Chemistry until 1946.

In 1947 he took an active part in the Centenary Celebrations of the Chemical Society. He was Chairman of an Exhibition at the Science Museum illustrating the achievements of British chemists during the last one hundred years and brought together a remarkable collection of apparatus of historical interest.

In 1948 he was appointed Editor in Chief of a comprehensive work on "The Science of Explosives," but after putting much work into this he was ultimately compelled by failing health to relinquish the Editorship.

He was practically free from illness until the early part of 1948, when he had a bad heart and congestion of the lungs. His tough constitution pulled him through, but he was much weakened. In 1949 he had influenza and broncho-pneumonia and passed away at his home in London on April 28th, just eleven days after his 80th birthday. He might almost be said to have died in harness, and I am sure he would not have wished it otherwise.

Thus ended a long and strenuous career. It was probably fortunate for him that he had to forge his way by hard work in his early years. From the beginning he strove after success and achieved it in a high degree. His honours included a presentation gold watch from the Secretary of State for War in recognition of gallant behaviour after a serious explosion in 1894, the Fellowship of the Royal Society in 1917, the K.B.E. in 1918, LL.D. St. Andrews in 1923, the Silver Jubilee Medal in 1935, the Coronation Medal in 1937 and the Davy Medal of the Royal Society in 1944.

In all that he undertook he worked tirelessly and conscientiously; his tenacity of purpose carried him through many difficulties. He was supremely self-confident, frequently autocratic and domineering. His tough constitution enabled him to retain his vigour into old age and his studious disposition remained with him to the end. He strove after recognition, but he had also his sentimental side; he was greatly attached to his old University and to his chemistry professor, and had many other intimate friends for whom he had a real affection.

International Relationships in Chemistry.—An account of Robertson's activities would be incomplete without some reference to his efforts to further co-operation and friendly intercourse with scientists abroad. As President of the Chemical Section of the British Association at Toronto in 1924 he made many lasting friendships. Whilst on the American continent he travelled to Vancouver and back, and then to the United States, where he established profitable

relations with our fellow-scientists. In 1927 he visited Paris as Royal Society representative at the Berthelot Celebrations and made a further visit in 1931. In 1930, and again in 1934, he visited Belgium and Northern France in connection with the problem of water-pollution. In 1934 he attended the International Congress of Chemistry at Madrid and in 1936 he visited Roumania, Istanbul, and Austria. In 1937 he went again to Paris for the Congress of Industrial Chemistry, and in 1938 he took part in the International Congress of Chemistry at Rome. He readily got on to a friendly footing with scientists abroad and in return he welcomed them on their visits to this country and showed them hospitality at his home. In so doing he rendered a real service to Science. With him national boundaries formed no barrier to the establishment of fraternal relations. During the war of 1939—1945 he was in very frequent contact with the Canadian and American representatives and did much to promote their co-operation.

In this connection the "Catalysts' Club" should be mentioned. It was established about thirty years ago, and one of its purposes was to entertain distinguished foreign visitors to this country having similar interests to those of the Club. Robertson took an active part in this and often presided at the meetings. The Club was well named and Robertson was distinctly a good catalyst. He was good company and, as one member put it, they liked his pawky humour.

Societies and Institutions.—Robertson's loyal devotion to the learned Societies was a feature which greatly impressed his colleagues and friends and he attended, and often presided at, a great number of scientific meetings.

Royal Society. Robertson was elected a Fellow in 1917. He served on a number of Committees, including the Committee on Applied Sciences (1919—1922) and the Committee for exhibit on Pure Sciences at the British Empire Exhibition (1922). He represented the Royal Society on the General Board and Executive Council of the N.P.L. (1925) and in the Berthelot Celebrations at Paris (1927). He was awarded the Davy Medal in 1944.

Chemical Society. He was elected as a Fellow in 1907 and was a Member of Council 1919—1922. He was a Vice-President in 1926—1929 and again in 1936—1939. In 1922 he represented the Chemical Society on the Conjoint Board of Scientific Societies. His activities in connection with the Centenary Celebrations are mentioned above.

Faraday Society. Elected 1920, he became a Member of Council in 1921 and was President in 1922—1924.

Royal Institution. Robertson was a devoted member of this Institution. He was elected in 1921, became Manager in 1924, Secretary 1926—1929 and Treasurer 1929—1946. During this time he acted as Vice-Chairman. When the renovation of the theatre and various building became urgent he took an active part in obtaining the necessary funds (about £100,000). During the Faraday Centenary Celebrations in 1931 he frequently presided at meetings.

British Association. Robertson was President of Section B (Chemistry) at the Toronto meeting of 1924.

Royal Institute of Chemistry. He became a Fellow in 1897, Member of Council 1915—1918 and 1921—1932, Vice-President 1918—1921.

Salters' Institute. Robertson was appointed Director in 1937 and continued to hold this post until shortly before his death.

London University. Member of Board of Studies for Chemistry and Chemical Industry 1921—1925 and 1944. Board of Advisors in Chemistry.

Ramsay Fellowships. Member of Advisory Committee 1921.

Ramsay Chemical Engineering Department. Member of Committee.

He was also a member of a number of other Scientific Societies and of the Royal Society Club and the Athenæum. His activities in connection with the St. Andrews University Club, London, have already been mentioned.

He maintained a close connection with the Scottish Universities through his position as Advisor in Physical Chemistry under the Carnegie Trust.

R. C. FARMER.

F. E. WHITMORE.

1923—1949.

FRANK EDWARD WHITMORE lost his life on July 25th, 1949, at the age of 26 in a climbing accident in Switzerland and his death came as a severe shock to his former teachers and to his colleagues and many friends in Birmingham.

Whitmore, one of three talented brothers, received his early education at Handsworth Grammar School from which he entered the Chemistry school of the University of Birmingham in 1942. Always a brilliant scholar, he duly graduated with first class Honours and was awarded a Teaching Scholarship in the Chemistry Department.

He engaged in research work under Dr. F. J. Llewellyn in the *X*-ray department, studying the single-crystal *X*-ray methods of determining the crystal structure of organic substances (explosives). With Llewellyn he published some of the work in the Journal (*J.*, 1947, 881).

On gaining his Ph.D. in 1946 he was appointed to an I.C.I. Fellowship which he held in the Department of Physics at Birmingham with the object of building up, with the unusual facilities available, a small group engaged in studying radiochemistry. In addition it was the object of his new group to look after general chemical problems of the Nuclear Physics laboratory and to provide a link with interested workers in the Chemistry Department. From the start, owing to his generous and helpful nature, this new venture was a marked success and in his researches Whitmore had already begun to make a name for himself. He was particularly interested in the chemical state of atoms newly formed by nuclear transformation, *e.g.*, in the cyclotron. He paid a good deal of attention to phosphorus 32, and showed that this element when made by the action of fast neutrons on the sulphur in sodium sulphide appears, when brought into aqueous solution, as a phosphate ion. Several papers on this work were in preparation for the press when he was killed.

His particular hobby was mountaineering and he was an enthusiastic, generous and able leader among Midland climbers. He had an unusual talent for amateur dramatics and in his undergraduate days was in great demand by the various University societies, particularly the University Chemical Society.

He was unmarried and leaves a widowed mother. Because of the long period of training necessary for such work, Whitmore's untimely end is a sad loss to radiochemistry and to Birmingham, and his place cannot easily be filled.

M. Stacey.

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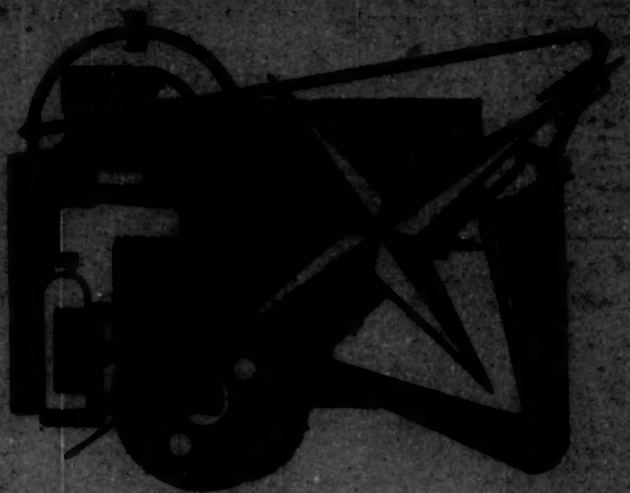

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